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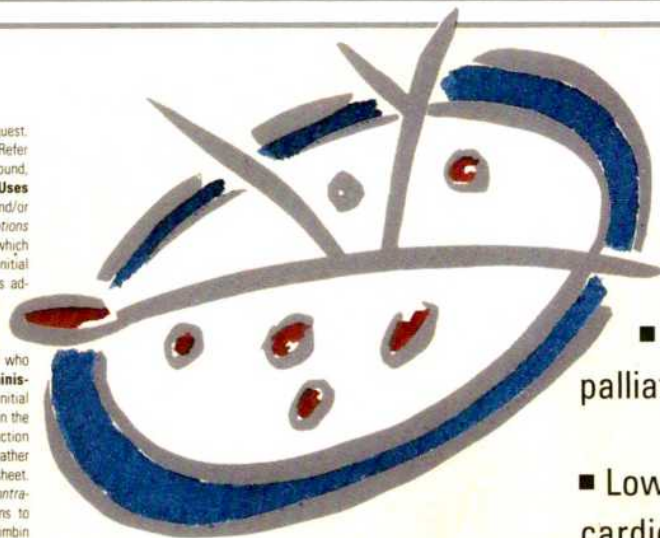
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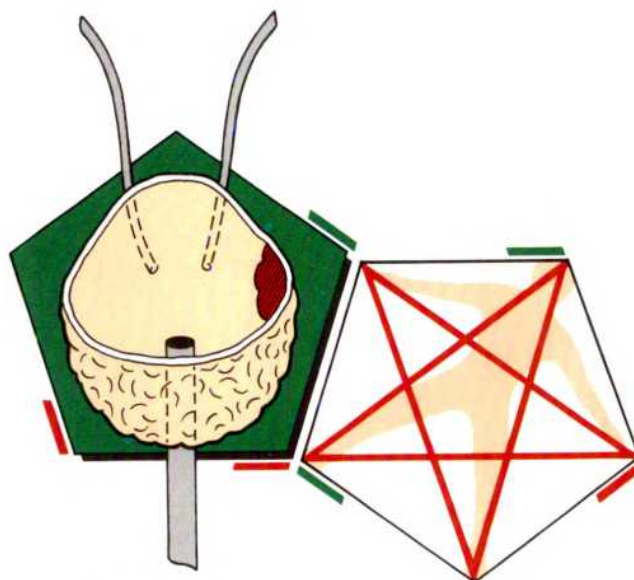
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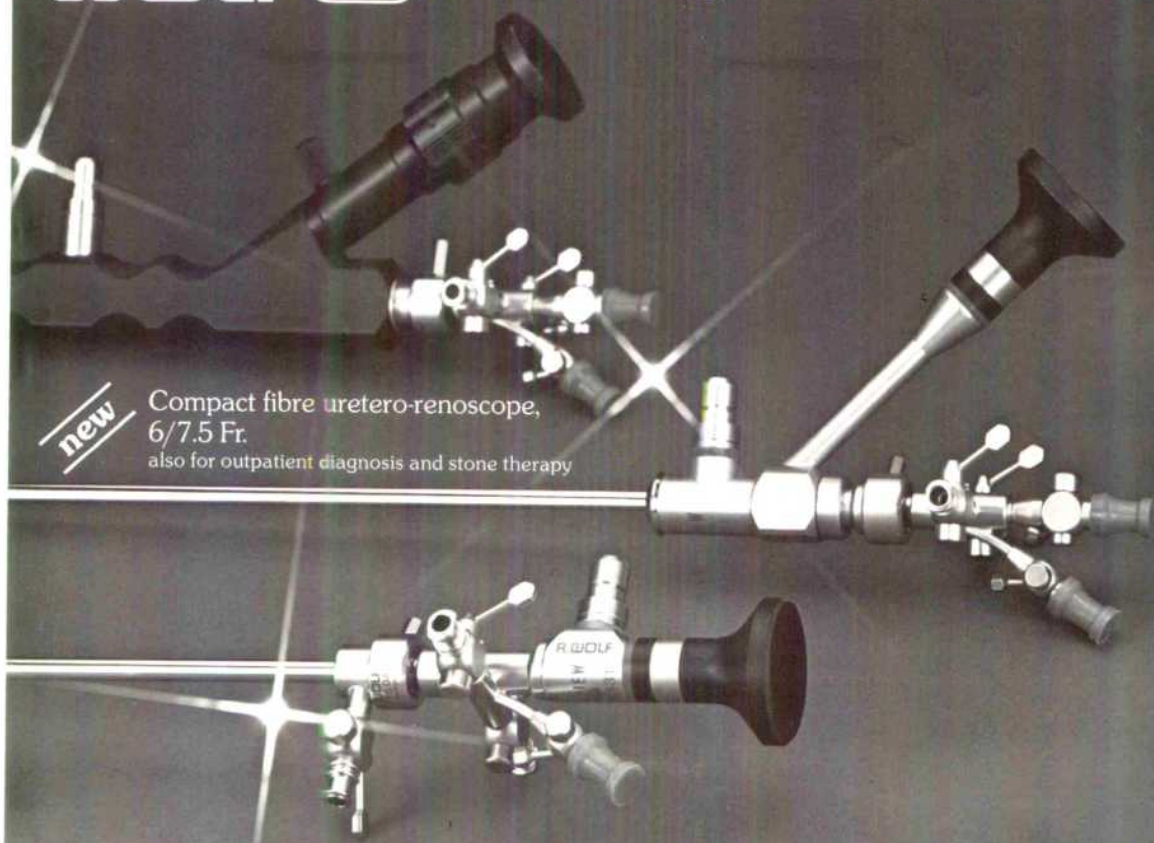
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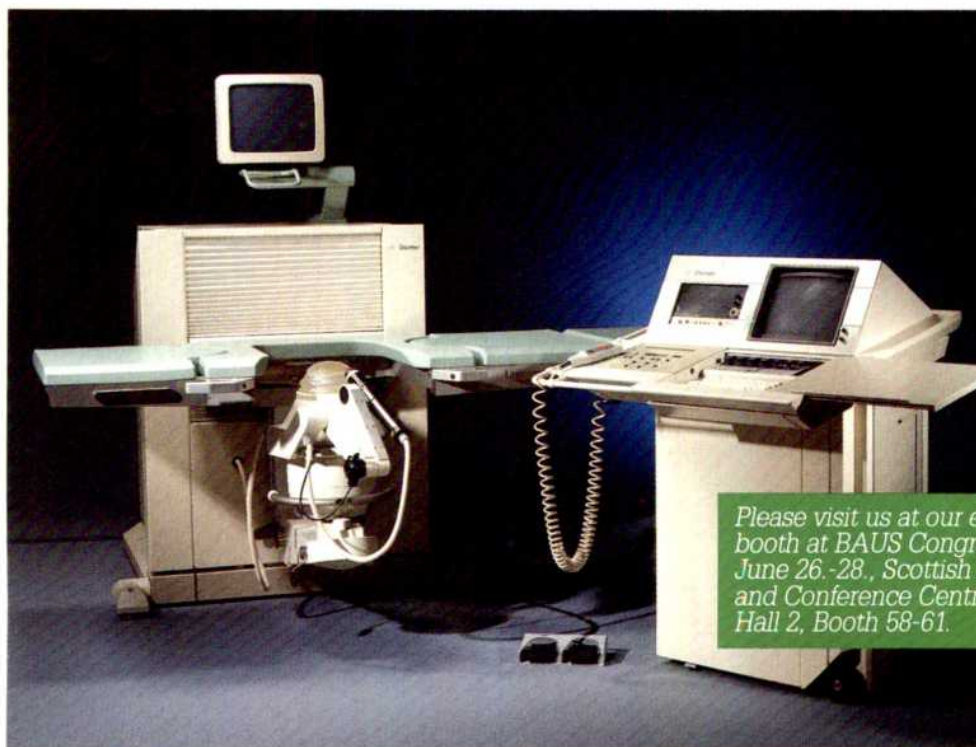
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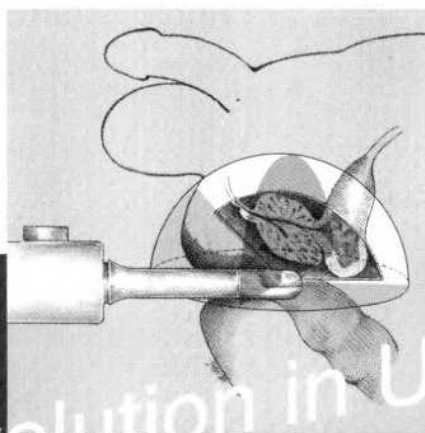
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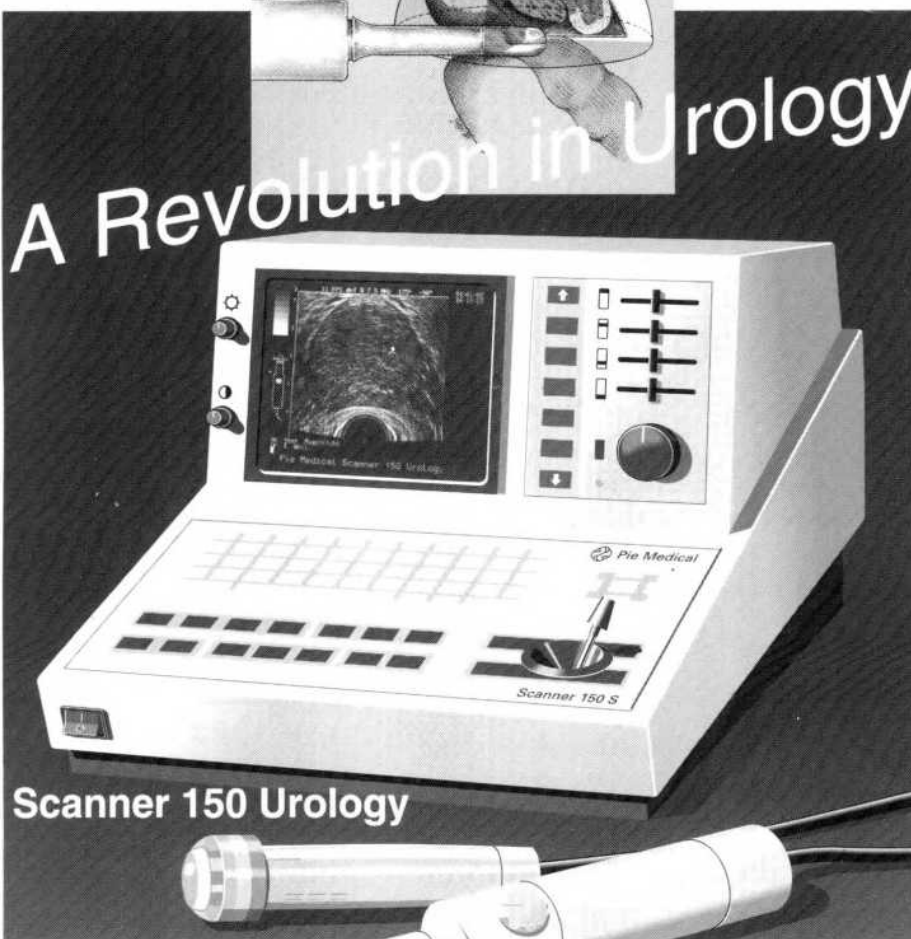


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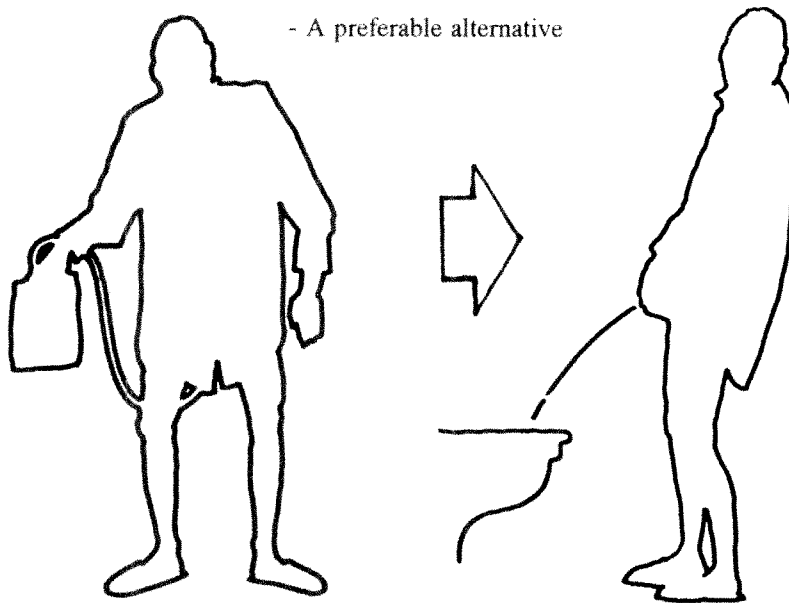
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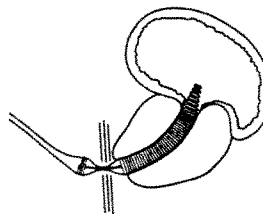
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REVIEW

Modern Paediatric Urology*

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The scope of paediatric urology was defined in the 1960s and the basic knowledge of disorders to be treated was also established at that time. In the 1970s there was a considerable increase in our understanding of the physiological aspects of urinary tract malformations. In addition, the contributions that were made to paediatric urology by other disciplines in medicine and science were more and more appreciated. For instance, in the late 1960s all children with any disorder vaguely associated with the urinary tract underwent an intravenous urogram and voiding cystogram. An interested group of radiologists, however, effected a change in these concepts: they emphasised non-invasive and more precise functional studies involving far less radiation. Thus the understanding, diagnosis and management of various disorders of the urogenital tract have been tremendously improved by ultrasonography, renography and renal scan techniques, urodynamics, CT scan and magnetic resonance imaging (MRI).

Obstructive uropathy and cystic kidneys are now frequently diagnosed prenatally by maternal ultrasonography (Reuss *et al.*, 1988; Livera *et al.*, 1989) and early treatment of obstructive uropathy is done all over the world. Nevertheless, for anomalies such as hydroureteronephrosis the benefit of early treatment is questioned, because spontaneous improvement has been reported in some cases, especially in the primary obstructive megaureter (Keating *et al.*, 1989). Therefore the recently founded European Society of Paediatric Urology instituted a committee to set up a prospective study on this topic.

The diagnosis, classification and treatment of

neurogenic bladder dysfunction have also been improved and, thanks to urodynamic studies, different patterns of bladder dysfunction can now be distinguished (van Gool, 1986). After the recognition of functional bladder outlet obstruction by detrusor sphincter dyssynergia, new models for the treatment of obstruction and incontinence were developed. With the advent and acceptance of clean intermittent catheterisation, sometimes in combination with anticholinergic treatment and bladder augmentation techniques, or implantation of an artificial sphincter prosthesis, the need for permanent urinary diversion in the paediatric age group has greatly diminished. Even reconstruction of a previously diverted urinary tract has become popular (Firlit *et al.*, 1980). However, undiversion is often a difficult and time-consuming operation which should be performed only by skilled surgeons in centres providing adequate intensive care. Moreover, the patients and parents should be well motivated and able to start clean intermittent catheterisation if necessary. Finally, they have to accept the possibility of a new diversion in case of failure of the undiversion (Scholtmeijer, 1984).

Anorectal malformations and oesophageal atresia are frequently associated with urological disorders (Hoekstra *et al.*, 1983; Berkhoff *et al.*, 1989) and only close co-operation between the paediatric surgeon and paediatric urologist will provide the best opportunity for a good quality of life for many patients. Apart from rectourethral and rectovaginal fistulae, anomalies of the urogenital tract are found in 50% of patients with anorectal malformations (Hoekstra *et al.*, 1983). Vesicoureteric reflux has been found in 47% of children with a supralelevator and in 35% with an infralevator lesion. Anomalies of the urogenital tract were noted in 21% of patients with oesophageal atresia and tracheo-oesophageal fistula. Prompt and appropriate investigation of the

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genitourinary tract by physical examination, urine analysis, serum creatinine levels, ultrasonography or intravenous urography, voiding cystourethrography, renal scan and urodynamic studies is recommended as a standard in all children with anorectal and tracheo-oesophageal malformations.

For children with ambiguous genitalia an immediate and multidisciplinary approach by a team consisting of a paediatric endocrinologist, paediatric surgeon, paediatric urologist and a child psychiatrist or psychologist is mandatory (Drop *et al.*, 1984). When the genitalia appear abnormal it is necessary to assess the newborn thoroughly and rationally in order to reach an assignment of gender concordant with how the child will best function anatomically and sexually. Apart from evaluation of the urogenital tract by ultrasonography or intravenous urography, genitography and vaginocopy/cystoscopy, a medical evaluation of serum electrolytes, renal function, serum steroids, urinary steroids and karyotype analysis should be done. Further studies are sometimes necessary, such as laparoscopy/laparotomy, HCG test, ACTH test, *in vitro* androgen binding studies and estimation of the basal values of the gonadotrophins (LH, FSH). The parents should be informed in understandable terms about the condition of their child and the subsequent course of action. Surgical corrections should be performed as soon as possible, but some aspects of surgery can be postponed, as for instance the formation or reconstruction of the vagina.

Hypospadias and epispadias repair with single-stage operations at an early age are very common now (de Vries and Debruyne, 1984) and for the so-called "hypospadias cripple" due to multiple unsuccessful operations, a satisfactory reconstruction of the urethra can be obtained with an autologous bladder mucosal graft (Ransley *et al.*, 1986).

Approximately 1% of the diseases in childhood are malignancies and some 20% of these malignancies arise in the urogenital tract (Klippel and Altwein, 1986). Nephroblastoma is the most common solid tumour in childhood and most children with a Wilms' tumour are between 3 and 7 years of age and equally divided between the sexes. Thanks to multidisciplinary treatment, particularly the combination of chemotherapy and surgery, a remarkable success rate has been obtained: the cure rate is approximately 75%, but for bilateral Wilms' tumours it is 50%. For rhabdomyosarcomas the results of treatment have improved dramatically as well, mainly because of multidisciplinary management and the advent of polychemotherapy. The prognosis seems to be better for rhabdomyosarcoma

of the bladder, with a survival rate of 70%, than for rhabdomyosarcoma of the prostate, with a survival rate of 50% (Scholtmeijer *et al.*, 1983). With modern pre-operative chemotherapy the tumour can be reduced considerably with fewer side effects, after which sparing surgery is possible in many cases. The same treatment policy is applicable to the sacrococcygeal teratoma (Ringert and Havers, 1988), so that surrounding organs may be spared and a better quality of life can be obtained.

Extracorporeal shock wave lithotripsy (ESWL), advances in fiberoptic technology, the development of smaller instruments for manipulation and improvements in available ureteroscopes have dramatically increased the therapeutic options available to the urologist for the treatment of calculus disease in children. ESWL is suitable even for small children with a minimal height of 70 cm, provided that there are no concomitant anomalies (e.g. pelviureteric obstruction or primary obstructive megaureter) which need surgery. Within 6 months 80% of the children treated with ESWL become free of stones and the need for auxiliary measures is very rare (Nijman *et al.*, 1989). Although ESWL has been extremely successful in the treatment of paediatric urolithiasis, it is important to remember that it is only one part of the complete treatment of patients with stones and that urolithiasis needs thorough metabolic and anatomical evaluation.

Urodynamic studies have not only improved the knowledge of neurogenic bladder dysfunction but have also changed the concepts of bladder neck sclerosis, distal urethral stenosis and vesicoureteric reflux. Primary bladder neck sclerosis is very rare and appears to occur in boys only. Obstruction at the level of the bladder neck and proximal urethra is mostly caused by overactivity of the urethral closure mechanism (Griffiths and Scholtmeijer, 1983), for which medical treatment can be given (Klippel and Altwein, 1986), sometimes in combination with clean intermittent catheterisation. Distal urethral stenosis in girls also appears to be very rare, and comparing the bougie à boule calibration with the urodynamically estimated calibre of the urethra there is a statistically significant and extremely close correlation between the 2 measurements. Stenoses calibrating at 14 F are apparently always urodynamically obstructive and those calibrating at 16 F are sometimes so, but stenoses calibrating at 18 F or more are urodynamically non-obstructive (Scholtmeijer and Griffiths, 1985).

Since 1983, attention has been directed towards

vesicoureteric reflux in children with no overt abnormality other than urodynamically demonstrable dysfunction of the lower tract. Not only a congenitally abnormal implantation of the ureter into the bladder or urinary tract infections, but also bladder or urethral dysfunction with development of high bladder pressures seem to be important in the development of reflux (Scholtmeijer and Griffiths, 1988a and b; Seruca, 1989). In the case of bladder instability the use of anticholinergic therapy reduces the need for surgical treatment, since reflux can be cured or diminished within 6 to 12 months by anticholinergic drugs plus antibacterial treatment, even in patients with grade IV reflux (Scholtmeijer and Griffiths, 1990). Therefore voiding cystourethrography is suitable only for the detection and classification of vesicoureteric reflux, but a urodynamic study is suggested for the decision on which treatment should be given. Moreover, some prospective studies have shown that surgery is hardly necessary in low grade reflux (Birmingham Reflux Study Group, 1987; Scholtmeijer and Griffiths, 1988a and b).

Paediatric urology is developing very quickly and it is clear that its basic requirements are not simply a small cystoscope and the complete apparatus of a children's surgical unit but also a complete training in urology, including urodynamics. Also required are knowledge of the specific physiological aspects of the child with regard to permissible blood loss during operations, administration of parenteral fluids, calculation of drug dosages, nutrition, etc.

To reach the highest standards of paediatric urology it is essential to co-operate closely with colleagues who have a special interest and training in paediatric radiology, nephrology, surgery, anaesthesiology, oncology, psychology and pathology. This is only possible in specialised centres with a well trained and experienced staff. In such centres complicated surgical procedures are now routinely performed in children with serious urological malformations, while more attention is also being paid to basic research in paediatric urology, with the aim of making a substantial contribution to modern paediatric urology.

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Characterisation of Inflammatory Cells Associated with “Idiopathic Retroperitoneal Fibrosis”

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Summary—During ureterolysis in a patient with “idiopathic retroperitoneal fibrosis”, fresh samples of peri-ureteric and peri-aortic tissue were obtained. An abdominal CT scan confirmed the peri-aortic distribution of the inflammation associated with advanced abdominal aortic atherosclerosis. Histology confirmed the presence of fibrosis and a variable chronic inflammatory cell infiltrate. Monoclonal antibodies were used to identify the inflammatory cells. B and T lymphocytes were present with the majority of T lymphocytes of the T helper phenotype. The majority of lymphocytes and macrophages and most vascular endothelial cells were HLA-DR positive. Ki67 and BerH2 staining was found in B cells and T helper cells, indicating that these cells were proliferating and activated. These findings compare with the characterisation of inflammatory cells associated with “inflammatory aneurysms” and with the inflammatory cells present in the spectrum of inflammation seen as a complication of advanced atherosclerosis—conditions known as “chronic peri-aortitis”. It is suggested that our findings support the view that idiopathic retroperitoneal fibrosis represents clinical chronic peri-aortitis seen in an undilated aorta.

A spectrum of chronic inflammation in the aortic adventitia frequently accompanies advanced atherosclerosis (Schwartz and Mitchell, 1962; Parums, 1990). Chronic peri-aortitis, which is associated with thinning of the media, is a term suggested for this condition (Mitchinson, 1984). Chronic peri-aortitis may be detected only histopathologically, usually at necropsy, or, in its most severe form, may present clinically in the form of idiopathic retroperitoneal fibrosis, peri-aneurysmal retroperitoneal fibrosis or inflammatory aneurysm (Walker *et al.*, 1972; Serra *et al.*, 1980; Mitchinson, 1986). In a recent review, Parums (1990) showed that there was no significant difference in their clinical presentation between patients with inflammatory aneurysm and idiopathic retroperitoneal fibrosis, apart from an increase in aortic diameter in the former, and suggested that these 2 conditions represent clinical forms of chronic peri-aortitis.

Immunoglobulin-secreting plasma cells in the aortic adventitial infiltrate occur in chronic peri-aortitis; this has been interpreted as evidence that

chronic peri-aortitis is due to an auto-allergic reaction to a component of the atherosclerotic plaque (Parums and Mitchinson, 1981). Ceroid, an insoluble polymer of oxidised lipid and protein, is found in all advanced atherosclerotic plaques (Mitchinson *et al.*, 1985). Immunoglobulin, predominantly IgG, is associated with ceroid in plaques in patients with severe chronic peri-aortitis (Parums *et al.*, 1986). Ceroid can be manufactured artificially by completely oxidising low density lipoprotein (LDL) (Ball *et al.*, 1985). Furthermore, antibodies to oxidised LDL and ceroid are always detectable in patients with severe, chronic peri-aortitis (Parums *et al.*, 1990a). The nature of the inflammatory cell population has been investigated using immunohistochemical techniques in a single case of severe chronic peri-aortitis presenting as an inflammatory aneurysm (Parums *et al.*, 1990b) and in 12 cases of chronic peri-aortitis of varying degree associated with advanced aortic atherosclerosis (Parums and Ramshaw, 1990; Ramshaw and Parums, 1990). The findings confirmed the presence of IgG-containing plasma cells in the aortic adventitia together with a predominant population

of B cells and T helper cells. Positive HLA-DR staining was shown by the majority of lymphocytes and macrophages and by some vascular endothelial cells and smooth muscle cells.

In view of the above findings, the present study was undertaken to investigate the nature of the inflammatory cell infiltrate associated with idiopathic retroperitoneal fibrosis. A panel of monoclonal antibodies to leucocyte markers was used in order to determine whether idiopathic retroperitoneal fibrosis, like inflammatory aneurysm and sub-clinical forms of chronic peri-aortitis, represents an immune response mediated by locally activated chronic inflammatory cells.

Patients and Methods

Case report

A 58-year-old male was admitted with a 4-month history of back and lower abdominal pain which radiated to the thighs, scrotum and penis, becoming worse when sitting or lying down. He had been impotent for 3 months and complained of anorexia with weight loss of 10 kg over the same period. The acute complaint was a 5-day history of vomiting. He had no urinary or bowel symptoms.

On examination the patient was clinically anaemic with a blood pressure of 180/100 mmHg. The abdomen was unremarkable on examination, but scrotal oedema and bilateral hydroceles were noted. Serum creatinine was 518 $\mu\text{mol/l}$, urea 13.8 mmol/l, potassium 3.2 mmol/l and haemoglobin 7.6 g/dl. The ESR was 100 mm/h.

Ultrasound showed bilateral enlargement of the kidneys (13.5 cm in length) with mild hydronephrosis, more marked on the right. Abdominal CT (Fig. 1) revealed calcified atheroma lining the aorta. A cuff of soft tissue

surrounded the aorta and encased the ureters. The aorta was not increased in diameter.

Two days after admission the patient became anuric and oedema of the legs was noted. Retrograde urograms showed medial deviation of both ureters with obstruction. A prolonged attempt was made to pass J stents; when this proved impossible a right nephrostomy was performed, restoring renal function. Oral prednisolone, 60 mg once daily, was commenced. During this period the patient was transfused with a total of 7 units of packed cells prior to operation.

At operation a hard, fibrous plaque was identified around the aorta and lumbar spine. Ureterolysis was performed and the ureters surrounded with omentum on the right side and pericolic fat on the left. Three biopsy samples were taken from around the left and right ureters and from around the peri-aortic mass.

Post-operative recovery was good with resolution of all symptoms. The patient was given intravenous hydrocortisone 100 mg *t.d.s.* for 5 days and then restarted on 60 mg oral prednisolone once daily. He was discharged 9 days post-operatively on 40 mg prednisolone once daily. On review 1 month later he was still symptom-free. Serum creatinine and electrolytes were normal and the ESR was 30 mm/h. Plans were made to reduce the prednisolone from 40 to 20 mg over 4 weeks.

Tissue Processing

Representative sections of each biopsy were processed for routine histopathology and immunohistochemistry by standard formalin fixation and paraffin embedding. Unfixed tissue for each biopsy was snap frozen in liquid nitrogen, sectioned and stained immunohistochemically. Paraffin and frozen sections were stained with monoclonal antibodies using the alkaline phosphatase anti-alkaline

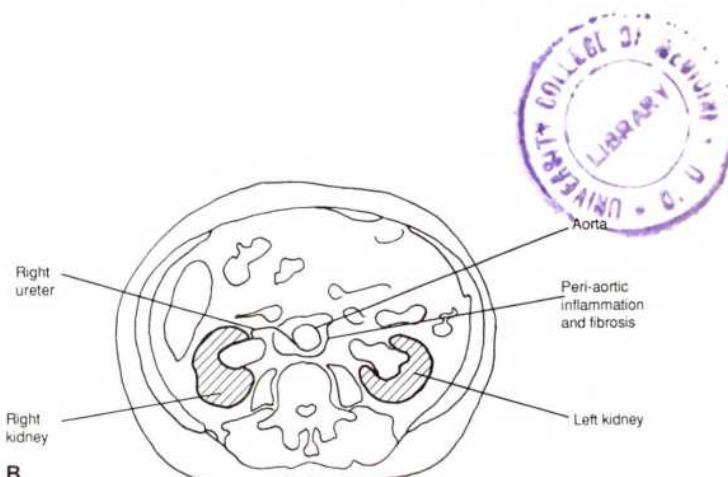
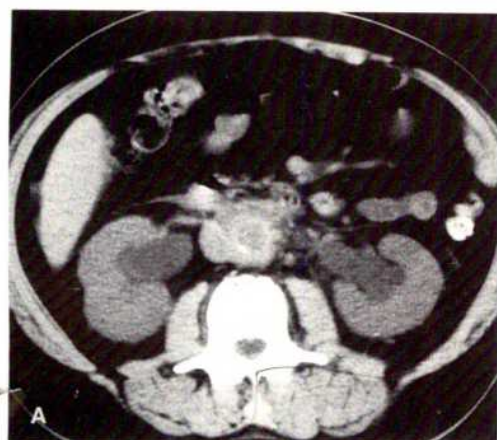


Fig. 1 (A) Pre-operative abdominal CT scan showing calcified atheroma lining the aorta with peri-aortic inflammation and fibrosis seen to involve the right ureter. Note the bilateral hydronephrosis. (B) Diagram of CT scan.

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phosphatase technique (APAAP) (Cordell *et al.*, 1984).

A panel of mouse monoclonal antibodies (Dakopatts a/s, Denmark) against human antigens was used which included those which could be used on paraffin sections: anti-human IgG, anti-human IgM, 4KB5 (B cell marker), UCHL1 (T cell marker) and those which could only be used on frozen tissue sections: T3-10 (T helper marker), Tü102 (T cytotoxic/suppressor marker), EBM11 (macrophages), TAL-1B5 (HLA-DR α chain), CR3/43 (HLA-DR β chain), Ki67 (nuclear antigen in proliferating cells) and BerH2 (CD30 on activated T and B cells). Routine electron microscopy was performed with sections stained with uranyl acetate and lead citrate before examination with a Phillips EM410 transmission electron microscope (Phillips, Eindhoven, The Netherlands).

Results

Routine light microscopy

The biopsies taken from around the right and left ureter and from the peri-aortic mass showed dense fibrous tissue containing abundant chronic inflammatory cells consisting of lymphocytes, plasma cells and macrophages with occasional lymphoid follicle formation (Fig. 2). Small blood vessels and vascular channels were abundant. Electron microscopy

confirmed the benign nature of the cellular components. There was no evidence of lymphoma, myeloma or carcinoma.

Immunohistochemistry

Immunohistochemistry revealed a mixed lymphocytic infiltrate of T cells and B cells with an increase in the ratio of T helper to T suppressor lymphocytes of approximately 4:1. Plasma cells were found to be secreting IgG with IgM to a lesser degree. The inflammatory cells were often surrounding blood vessels with "high" endothelial cells. Blood vessels were also seen in the absence of surrounding lymphocytes. B cells comprised approximately 40% of the lymphocytes and were grouped in dense focal areas. T cells comprised approximately 60% of the total lymphocytes. T cells surrounded B cell areas, but were also more dispersed than the B cells; they were often found as single cells outside B cell areas. Macrophages were found in abundance.

All macrophages and most lymphocytes were HLA-DR positive (Fig. 3), as were most vascular endothelial cells, suggesting that these cells were involved in antigen presentation in an immune based reaction.

Ki67 staining was found in groups of cells in B cell areas and in cells individually dispersed in T helper areas, indicating that these cells were proliferating. Positive staining with Ki67 was seen

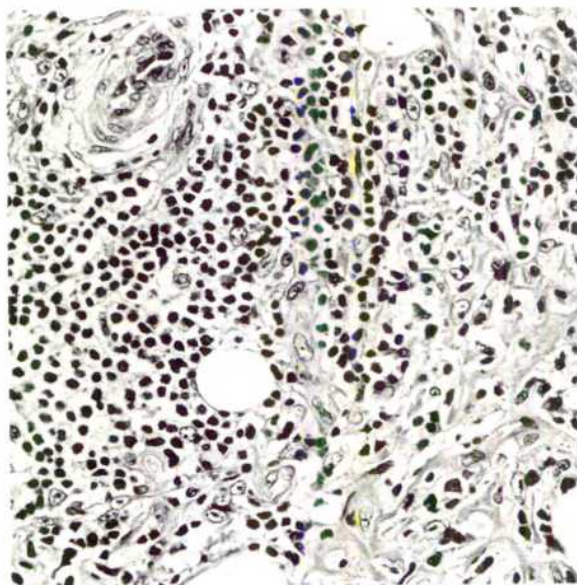


Fig. 2 Biopsy from tissue around the right ureter. Note the dense fibrous tissue containing a mixed chronic inflammatory cell population consisting of lymphocytes, plasma cells, macrophages and endothelial cells. (H and E $\times 25$).

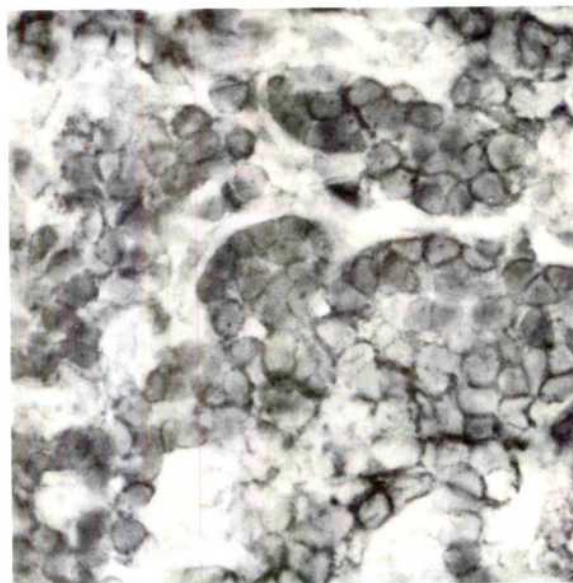


Fig. 3 Fresh tissue taken from the peri-aortic mass. The positive staining shown here is with the mouse monoclonal antibody, Tal-1B5, showing that lymphocytes are expressing MHC Class II antigen. Counterstained with haematoxylin $\times 60$.

with increasing frequency in areas with more severe inflammation and in areas with lymphoid follicles. BerH2 staining was found in some lymphocytes, more commonly in the most inflamed tissues, indicating that lymphocytes were activated.

Discussion

Chronic peri-aortitis is a condition which is seen as a spectrum of chronic inflammation secondary to advanced atherosclerosis (Parums, 1990). In its severest form, chronic peri-aortitis may present in undilated aortas, as in this case, and may be referred to clinically as idiopathic retroperitoneal fibrosis. This is an unsatisfactory term because it perpetuates the image of a disease of unknown cause, arising from somewhere in the retroperitoneum. As this present case has illustrated, and as other workers have shown (Dalla-Palma *et al.*, 1981; Dixon *et al.*, 1984; Mitchinson, 1986; Baker *et al.*, 1988), the typical form of this condition has a peri-aortic origin, the aorta is atherosclerotic and fibrosis is a variable component of the inflammation seen.

The histology from this case showed peri-aortic fibrosis and chronic inflammation, consistent with the diagnosis of chronic peri-aortitis (Mitchinson, 1984). Computed tomography (CT) showed a characteristic peri-aortic cuff of inflammation. This method can usually distinguish chronic peri-aortitis from malignant infiltrations, including those involving the para-aortic lymph nodes. CT is invaluable in distinguishing between chronic peri-aortitis and true retroperitoneal disease such as post-radiation fibrosis, sarcoma, endometriosis and fibrosis secondary to diverticulitis. Although desirable, CT is not essential for the diagnosis of idiopathic retroperitoneal fibrosis. When the disease is suspected, the urographic findings of medial deviation of 1 or both ureters with complete or partial obstruction, usually at the level of L3 or L4 vertebra, are virtually diagnostic. The ESR usually exceeds 45 mm/h and is often much higher (Mitchinson, 1972). Chronic peri-aortitis, without ureteric involvement, is usually only discovered at operation on aortic aneurysms if CT has not been used.

CT is also of value in the follow-up of patients with idiopathic retroperitoneal fibrosis who are treated with steroids (Brooks *et al.*, 1987). The rapidity of the response to steroids seen in patients with ureteric obstruction suggests that the ureter is not blocked by fibrosis but rather by oedema and inflammation. The successful long-term use of steroid therapy supports the view that chronic peri-

aortitis is a disease of immune rather than infectious origin. Brooks *et al.* (1987) showed that the peri-aortic mass may shrink even without steroid therapy and suggested that the mass in chronic peri-aortitis shrinks as part of its natural history, being more cellular in its early stages and containing more fibrous tissue in its later stages, contracting as it does so. This would explain how mobile structures such as the ureters may be dragged medially towards the aorta.

The results of the present study confirm and extend those previously reported in a single case of severe chronic peri-aortitis which presented as an inflammatory aneurysm (Parums *et al.*, 1990b) and in 12 cases of sub-clinical chronic peri-aortitis of varying degree associated with advanced abdominal aortic atherosclerosis (Ramshaw and Parums, 1990). The finding of Ki67 and BerH2 staining of lymphocytes in the aortic adventitia in chronic peri-aortitis indicates that the inflammatory process is an active immunological phenomenon and not a non-specific chronic inflammatory process secondary to some tissue damaging event.

Chronic peri-aortitis is characterised by the presence of adventitial mononuclear cells together with a varied amount of peri-aortic fibrosis. What determines the degree of fibrosis is unknown, but in its severest form it is this fibrotic reaction which leads to the clinical manifestations of the disease, such as ureteric obstruction. Cells of the immune system are known to be sources of mediators regulating fibroblast proliferation (Freundlich *et al.*, 1986). The macrophage is a source of fibroblast growth factor (Leibovich and Ross, 1976) and the T lymphocyte is known to produce fibroblast growth factor and collagen synthesis stimulatory factors (Wahl and Gately, 1983). Studies are presently under way to investigate the nature of these inflammatory mediators.

It is hoped to extend these findings by examining more biopsy specimens from patients with a spectrum of chronic peri-aortitis who present surgically. Both *in situ* immunohistochemical studies and *in vitro* cell culture studies are presently in progress.

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Value of the Patient's Case History in Diagnosing Urinary Incontinence in General Practice

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Summary—What is the value of the case history in diagnosing urinary incontinence in general practice? A total of 103 women with urinary incontinence presented to their general practitioner (GP) and underwent a standard history-taking, physical examination and urodynamic testing. The urodynamic diagnoses were analysed against symptoms and symptom complexes. Symptoms of stress incontinence in the absence of symptoms of urge incontinence had a sensitivity of 78%, specificity of 84% and predictive value of 87%. Symptoms of urge incontinence in the absence of symptoms of stress incontinence excluded genuine stress incontinence.

Information on age, parity, enuresis, nocturia, frequency, urgency, cystocele, prolapse and hysterectomy did not contribute to a correct diagnosis.

It was concluded that urodynamics are unnecessary in most women presenting with urinary incontinence in general practice.

Urinary incontinence is a common health problem, particularly among women (Jolleys, 1988). An accurate diagnosis is important, since errors may expose patients to inappropriate and unnecessary therapy.

Most contemporary reports claim that urinary symptoms are poor indicators of the underlying cause of incontinence and therefore advocate diagnostic urodynamic evaluation (Faber *et al.*, 1983; Karl and Hannappel, 1983; Byrne *et al.*, 1987; Korda *et al.*, 1987; Maes and Wyndaele, 1988; Sand *et al.*, 1988; Vereecken and Wouters, 1988; Walters and Shields, 1988). The urodynamic findings are considered essential to objective diagnosis. However, these studies were based on patients referred (*i.e.* selected) to hospital for treatment and probably included more complex and more serious cases than those encountered in routine general practice.

Effective diagnosis in the setting of general practice is of great importance in view of the high prevalence of incontinence and the fact that urodynamic investigations are not readily available to general practitioners.

The aim of this study was to assess the diagnostic value of the patient's medical history in distinguishing between genuine stress incontinence, detrusor instability and mixed incontinence in primary care. What are the most relevant symptoms of micturition in this respect?

Patients and Methods

Between January 1987 and January 1990, 13 general practitioners selected female patients presenting with urinary incontinence for the study. They were aged between 20 and 65 years. Women were excluded if any of the following factors were present: a previous operation for incontinence; underlying neurological aetiology for incontinence; diabetes mellitus; a temporary cause for incontinence (pregnancy, bed rest); urinary tract infection. Microscopy, followed by a urine culture in case of doubt, was performed in every patient to exclude urinary tract infection.

Incontinence was defined as the involuntary loss of urine twice or more times per month. All patients selected were examined by the same GP researcher (A.L.M.L.). The examination included a questionnaire on micturition symptoms to provide infor-

mation on the type of incontinence (Table 1). Abdominal and vaginal examination was performed with special attention to the presence of cystocele and prolapse. All patients underwent a complete urodynamic evaluation (static and dynamic urethral pressure profiles, cystometry, uroflowmetry). All urodynamic tests were performed by the same specialised and experienced nurse and the standard criteria of the International Continence Society were applied.

The following definitions were used.

Urgency: strong desire to void.

Frequency: voiding more than 10 times per day.

Nocturia: the need to get out of bed to void more than twice a night.

Enuresis: wetting the bed above the age 7 years.

The symptom 'stress incontinence' is the loss of urine during coughing and/or sneezing; 'urge incontinence' is the involuntary loss of urine associated with a strong desire to void (Table 1).

In the statistical analysis the history and urodynamic diagnosis were compared, using the urodynamic diagnosis as the criterion for the type of incontinence. The analysis included both single micturition symptoms and symptom complexes. A logistic regression analysis was used to examine which of the following factors, apart from micturition symptoms, contributed significantly to distinguishing the various types of incontinence: age, parity, enuresis, prolapse, cystocele, hysterectomy. The ability of the history to predict correctly the urodynamic diagnosis was expressed in sensitivity, specificity and predictive value.

Sensitivity (the chance of an abnormal finding in case of illness) indicates the rate of an abnormal micturition history corresponding to the presence of the type of incontinence in question.

Specificity (the chance of normal findings in healthy persons) indicates the rate of a normal micturition history corresponding to the absence of the type of incontinence in question.

Predictive value indicates the rate of true patients among those with a positive test (positive predictive value) or the rate of false patients among those with a negative test (negative predictive value).

The study was approved by the Medical Ethics Committee of the University of Nijmegen. The women were informed about the study design and they agreed to the terms.

Results

Of the 110 women in the study, 7 refused to undergo urodynamic investigation (response 94%). The majority of patients were aged between 35 and 54 years. Genuine stress incontinence was found in almost 60% of the patients, with only 6 having no demonstrable incontinence on urodynamics. In 69% there was complete agreement between the history and urodynamic findings (Table 2). The following 2 symptom complexes appeared to be the most important in discriminating between the diagnostic groups: (1) the presence of stress incontinence in the absence of urge incontinence had a sensitivity of 78% and a specificity of 84% for genuine stress incontinence; (2) the presence of urge incontinence in the absence of stress incontinence excluded the possibility of genuine stress incontinence and had a high specificity for detrusor instability. Symptoms of both stress and urge incontinence were poor predictors of mixed incontinence (Table 3).

Urgency, frequency and nocturia, whether present or absent, were very imprecise symptoms in diagnosing the type of incontinence. Age, parity, enuresis, prolapse, cystocele and hysterectomy did not contribute to a correct diagnosis (Table 4).

Table 1 Questionnaire

1. Do you lose urine by spurts during coughing, sneezing, jumping or lifting? (stress symptom).
(Y/N)
2. Do you have to urinate more than ten times during the day? (frequency).
(Y/N)
3. Do you have to get out of bed to void urine more than twice a night? (nocturia).
(Y/N)
4. Do you usually have a strong desire to void? (urgency).
(Y/N)
5. Do you have such a strong desire to void that you leak before reaching the toilet? (urge symptom).
(Y/N)

Table 2 History versus Urodynamic Diagnosis

History	Urodynamic diagnosis			
	GSI	DI	GSI + DI	No incontinence
Stress incontinence	47	1	4	2
Urge incontinence	—	11	2	2
Mixed incontinence	12	5	13	1
Others	1	1	—	1
Total (n = 103)	60	18	19	6

GSI = Genuine stress incontinence.

DI = Detrusor instability.

GSI + DI = Mixed incontinence.

Table 3 Sensitivity, Specificity, Predictive Values of Incontinence Symptom Complexes

	<i>Stress incontinence*</i>		<i>Urge incontinence†</i>		<i>Mixed incontinence‡</i>	
	%	CI ⁺	%	CI	%	CI
Sensitivity	78	± 11	61	± 23	68	± 21
Specificity	84	± 11	95	± 5	79	± 9
Positive predictive value	87	± 9	73	± 23	42	± 18
Negative predictive value	73	± 13	92	± 6	92	± 7

* A history of involuntary urine loss during stress and the absence of the symptom urge incontinence (Yes to question 1 and no to question 5)

† A history of the presence of the symptom urge incontinence and the absence of the symptom stress incontinence (Yes to question 5 and no to question 1).

‡ A history of involuntary urine loss during stress and the presence of the symptom urge incontinence. (Yes to both questions 1 and 5).

CI⁺ = Confidence intervals.

Discussion

Incontinence is a common problem in general practice and challenges the general practitioner to provide adequate therapy. It has been reported that incontinence can be successfully managed in general practice (Jolleys, 1989). Whether extensive diagnostic testing is necessary remains an open question, since most studies are based on populations selected for specialist care. Detrusor instability and mixed incontinence form a substantial part of these populations. The women in this study presented to their GP with incontinence and the majority had genuine stress incontinence. This finding supports the idea that the value of common tests for common diseases should be established in general practice.

The diagnosis "incontinence" and the type of incontinence were objectively confirmed in this study by urodynamic evaluation. Some doubt can be cast on this criterion, since 6 women had to be

classified as "having no incontinence". All 6 experienced an involuntary loss of urine at least twice a month and no alternative diagnosis could explain this symptom.

History-taking and urodynamic testing were performed by 2 different people, each unaware of the other's conclusions. This study was "observer-blind" in this respect. Since all of the histories were taken by one GP, this study does not provide information on inter-observer variation. The interpretation of the standard history, however, seems straightforward and few problems should be expected.

It is concluded that a standard history provides valuable information on the diagnosis of incontinence and is particularly helpful in distinguishing between genuine stress and other types of incontinence. If women complain of the involuntary loss of urine when coughing or sneezing, without urge symptoms, there is a high probability of genuine stress incontinence. They can be treated with pelvic floor exercises in a general practice setting. A history of isolated urge incontinence is a fair predictor of detrusor instability and bladder training can be started for these women. In both cases there is no need for further diagnostic investigations. These findings have been reported by others (Farrar *et al.*, 1975; Glezerman *et al.*, 1986; Hastie and Moisey, 1989). In this respect 2 questions are of great importance: "Do you lose urine by spurts during coughing, sneezing, jumping and lifting?" and "Do you have such a strong desire to void that you leak before reaching the toilet?". If these guidelines are applied, 1 in 5 patients will be inappropriately treated with pelvic floor exercises. This need not cause too much concern, for the treatment does not harm the patient and its

Table 4 Logistic Regression Procedure to Establish the Type of Incontinence. Dependent variable: type of incontinence

	Beta	χ^2	P	R
Intercept	-3.08244858	0.54	0.4618	
Age	-0.68399223	2.09	0.1486	-0.025
Parity	0.51524817	0.43	0.5124	0.000
Hysterectomy	-0.82583078	0.61	0.4344	0.000
Enuresis	-0.71996731	0.45	0.5015	0.000
Cystocele/prolapse	-0.31695295	0.23	0.6347	0.000
Stress symptom question 1	3.09499640	6.26	0.0124*	0.177
Frequency question 2	-0.13200707	0.04	0.8510	0.000
Nocturia question 3	0.64454976	0.68	0.4100	0.000
Urgency question 4	-1.05393417	1.95	0.1625	0.000
Urge symptom question 5	2.14931233	9.58	0.0020*	0.236

inadequacy will soon be obvious. The patient can be referred for urodynamic testing in due course. Urodynamic evaluation can be restricted to patients whose history reveals symptoms of both stress and urge incontinence.

A history of enuresis is often regarded as an indicator of detrusor instability (Korda *et al.*, 1987; Vereecken and Wouters, 1988; Walters and Shields, 1988). We are unable to confirm this, since only 14% of our patients mentioned it. Genuine stress incontinence and cystocele and prolapse may be associated (Faber *et al.*, 1983; Walters and Shields, 1988). A cystocele and/or prolapse were present in 35% of the women in this study. This is in accord with the findings in other studies (Faber *et al.*, 1983; Lagro-Janssen, 1986; Walters and Shields, 1988). Nevertheless, the presence of a cystocele and prolapse did not differentiate between various types of incontinence in this study.

It was concluded that a simple standard history is valuable in general practice to distinguish between genuine stress and other types of incontinence and to select patients (particularly those with both stress and urge symptoms) for comprehensive urodynamic investigation.

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Urethral Pressure and Power Generation during Coughing and Voluntary Contraction of the Pelvic Floor in Healthy Females

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Summary—A probe which permits continuous measurement of the related values of pressure and cross-sectional area in the female urethra was used to provide a quantitative description of the adjunctive occlusive forces in terms of pressure and power (mWatt) generation. Measurements were carried out at the bladder neck, midurethrally and distally in the urethra in 30 healthy women during coughing and squeezing.

Statistically significant variations were found in pressure and power generation between the 3 sites of measurement both during coughing and squeezing. Power generation and the pressure increase were significantly greater during coughing than during squeezing along the entire length of the urethra. The presence of a dynamic active closure mechanism was demonstrated at the bladder neck in addition to that located midurethrally. This bladder neck mechanism is thought to be due to the vagino-levator sling system (the urethral supports).

The maintenance of urinary continence during bladder filling even during increases in intravesical pressure requires (1) permanently and adjunctively acting closure forces tending to produce apposition of the urethral walls, (2) sufficient flexibility of the urethra to allow these closure forces to operate and (3) a mucosa-sealing secretion to block any remaining spaces (Zinner *et al.*, 1976; Griffiths, 1984).

The adjunctive urethral closure mechanisms, which act mainly during stress episodes, consist of passive transmission of intra-abdominal pressure and active pressure generation from the contraction of intramural and periurethral striated muscles (Enhörning, 1961). These 2 mechanisms combine to augment the occlusive forces of the urethra during stress conditions. To date, assessment of the adjunctive closure forces has been obtained mainly by means of pressure measurements in the urethra (Enhörning, 1961; Plante and Susset, 1980; Constantinou 1985). Dynamic (cough) pressure measurements require a microtip transducer technique because of the high frequency response (Hilton and

Stanton, 1983; Massey *et al.*, 1987). However, it is difficult to interpret data obtained by a conventional microtip transducer catheter because of artefacts such as directional differences in the urethral pressure (Constantinou, 1985; Plevnik *et al.*, 1985; McNally *et al.*, 1987; Schäfer, 1989).

A probe had been developed to measure the related values of pressure (P_{ure}) and cross-sectional area (CA) of the urethra under static and dynamic conditions (Lose *et al.*, 1986, 1988). This method permits accurate assessment of the power (mWatt) created by the adjunctive occlusive forces at different sites in the urethra during coughing and voluntary contraction of the pelvic floor. The aim of this study was to quantitate the adjunctive closure forces of the urethra by measuring urethral pressure and power generation during coughing and voluntary contraction of the pelvic floor in healthy females.

Methods

Pressure/Cross-sectional area probe

The probe (Fig. 1), which has been described previously (Lose *et al.*, 1986, 1988), enables simul-

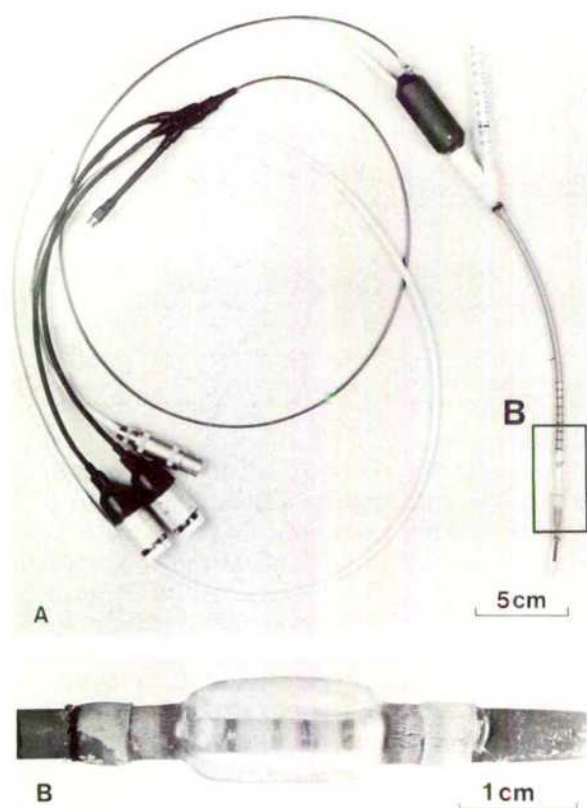


Fig. 1 (A) Probe for simultaneous measurement of urethral pressure cross-sectional area of the urethra and bladder pressure. The balloon is fully inflated. (B) The 4 ring electrodes can be seen inside the balloon.

taneous measurement of CA, P_{ura} and intravesical pressure (P_{ves}).

CA is induced by means of a cylindrical balloon (length 1.5 cm, diameter 1.0 cm) and measured according to the field gradient principle as modified by Colstrup *et al.* (1983). This implies that the impedance of the fluid in the balloon to a high frequency alternating current is inversely proportional to the CA of the balloon, and hence to the CA of the tube where the balloon is placed. The probe measures the average CA of a 2-mm segment of urethra in the range of 13–79 mm². Maximum CA can be induced in approximately 50 ms (Lose *et al.*, 1986).

Pressures are measured with a double microtip transducer (Honeywell). The proximal pressure sensor is placed in the balloon to measure the P_{ura} and tip sensor measures the P_{ves} . The rise time of the pressure system is 2.5 ms, corresponding to a frequency response of 189 Hz (Lose *et al.*, 1986).

Before each measurement the pressure sensors and the CA measuring unit were calibrated and the system tested to ensure it was free of air bubbles and without leakage. The probe was sterilised in Corsolin 3%.

Volunteers

The study group comprised 30 healthy female volunteers (median age 42 years, range 25–74) with no gynaecological or urological complaints. None had previously undergone urogenital surgery. The median parity was 2 (range 0–4); 23 women had normal menstruation and 7 were post-menopausal. Pelvic examination was normal in all cases, urine was sterile on culture and spontaneous uroflowmetry was normal. Urethral profilometry using an 8F perfusion catheter (perfusion rate 2 ml/s) with 2 side-holes revealed a median functional profile length of 32 mm (range 23–45).

All volunteers were informed of the purpose and methodology of the study and all gave informed consent. The study was approved by the regional Ethical Committee.

Investigative procedures

All measurements were performed as illustrated in Figure 2 with the subject in the supine position and with an empty bladder. Electromyography (EMG) was recorded with surface electrodes inserted in the vagina just behind the midurethra (Lose *et al.*, 1987). Before insertion the distal part of the probe was dipped in lignocaine jelly. The probe was placed with the 2 microtip transducers in the bladder and its position and the pressure transmission were verified by asking the subjects to cough. To avoid reflex activity during measurement, recordings were not initiated until 5 min after insertion of the probe. Measurements were performed with the CA-sensing electrodes located at 3 different positions in the urethra: (a) at the bladder neck (0.75 cm from the urethrovesical junction), (b) midurethrally (in the high pressure zone) and (c) distally (0.75 cm from the external meatus). The bladder neck was identified by placing the probe with the balloon in the bladder. The balloon was then inflated to its CA_{max} and the probe was retracted until the balloon entered the urethra as indicated by a marked increase in pressure. The high pressure zone was identified by retracting the balloon slowly through the urethra while connected to a reservoir providing a constant pressure. The high pressure zone was located at the site where the CA of the balloon was minimal. The distal site of measurement was identified by retracting the

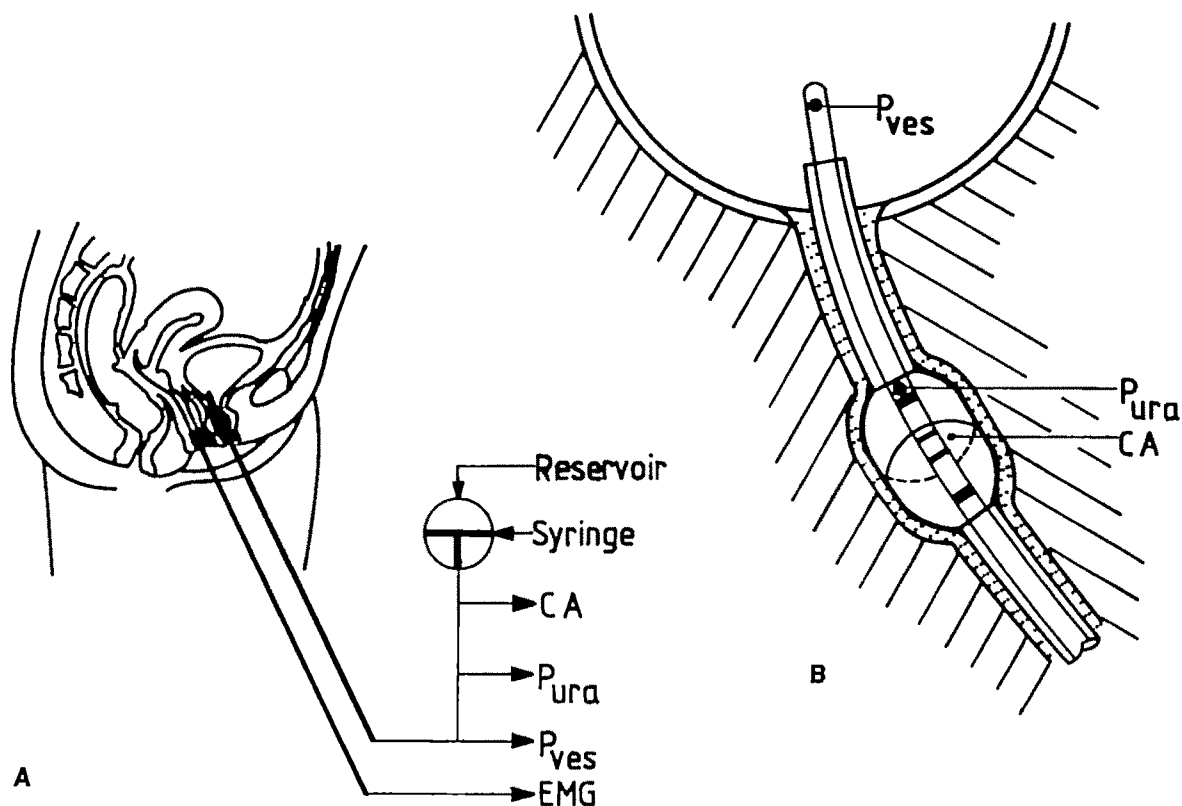


Fig. 2 Schematic drawing of the set-up for measurement in the female urethra (A) Urethral pressure (P_{ure}) and vesical pressure (P_{ves}) are measured with a double-tip transducer. Cross-sectional area (CA) is measured by means of the field gradient principle. CA is induced with a 1-ml syringe or from a reservoir. EMG is registered with surface electrodes in the vagina (B) The probe placed in the urethra. CA is measured between the 2 medial ring electrodes corresponding to a 2-mm slice of the urethra

balloon until it could be seen at the meatus. At each position the following procedure was carried out. After induction of a CA of about 50 mm² each subject was asked to cough and then to squeeze (hold urine) 3 times. The most vigorous cough and squeeze were used to calculate the power of contraction. During these manoeuvres, related values of CA and P_{ure} were recorded with the balloon open to a reservoir to allow for emptying of the balloon (Fig. 3). P_{ure} at rest and the pressure increase (ΔP_{ure}) during coughing and squeezing were measured at a fixed CA of approximately 20 mm² (Fig. 4). During coughing and squeezing the catheter was fixed manually at the external urethral orifice. All measurements were performed by the same investigator (G.L.).

The work (W) produced by the urethra to deflate the balloon is the volume reduction (dV) of the balloon multiplied by the maximum pressure in the balloon (P_{ure}), i.e. $W = P_{ure} \times dV$. If the balloon is assumed to be cylindrical with a length of 0.01 m,

the volume can be expressed as $CA \times 0.01$ (m³). The work produced by voluntary contraction of a cylindrical segment with the length of 0.01 m with uniform properties would be $W = P_{ure} \times dCA \times 0.01$ (kPa $\times$ m² $\times$ m = joule; 1 kPa = 10 cm H₂O). Since the duration of work can be read from the tracing, the power (joule/s = watt) of the contraction can be calculated. Power was used as a parameter instead of work since power expresses how fast work is performed and thus reveals more about the dynamic properties of the adjunctive occlusive forces.

Statistical methods

Statistical analysis was based on standard parametric methods (Diem and Lentner, 1975). Urethral pressure was found to have a normal distribution while power did not. However, after logarithmic transformation normality could be confirmed for the power data. Differences between the 3 sites of measurement were tested using analysis of variance (ANOVA). This permitted separation of the total

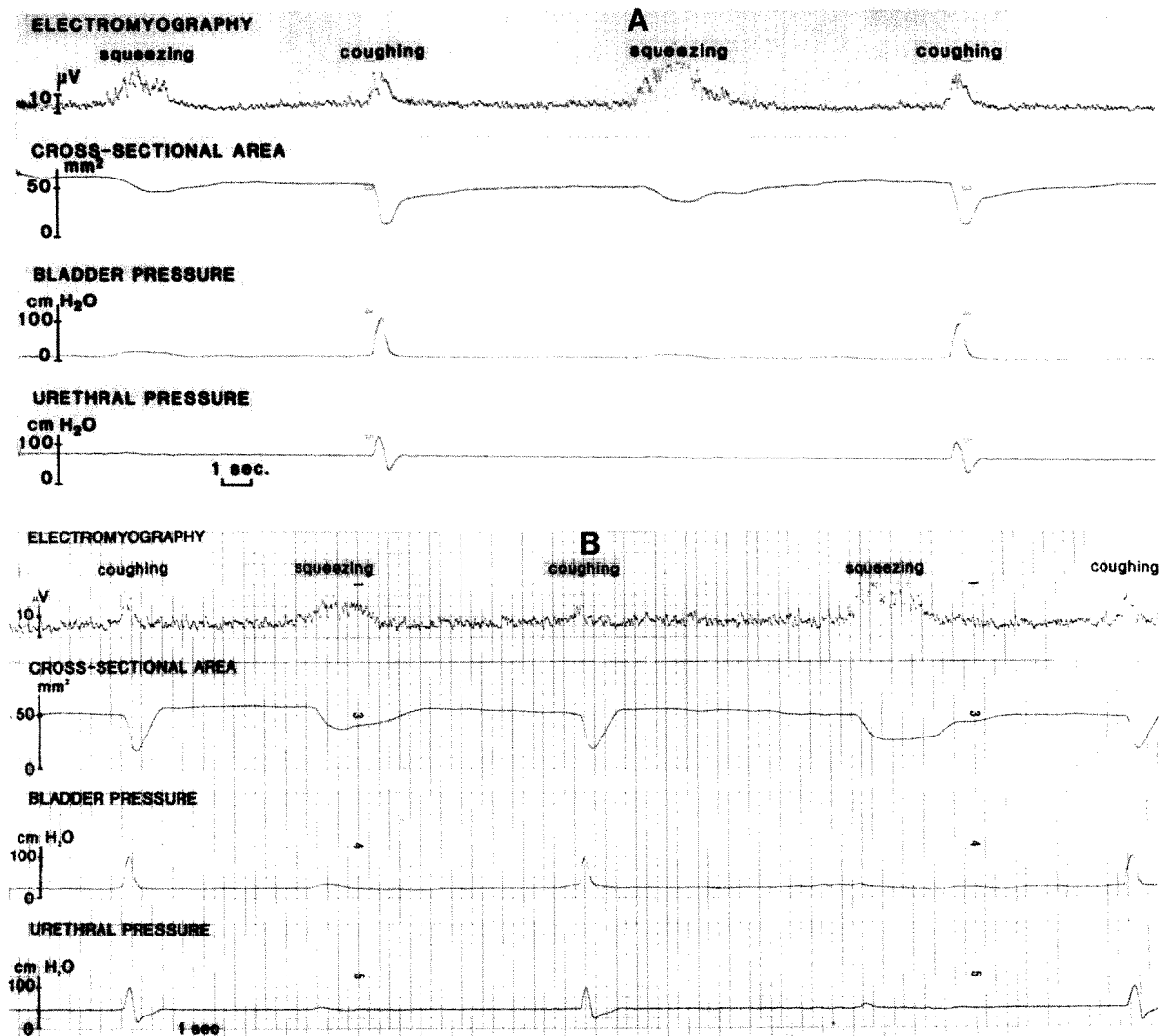


Fig. 3 (A) Measurement of cross-sectional area (CA) in the urethra after induction of a constant pressure of 75 cm H₂O and the CA pressure changes during squeezing and coughing. The pressure was induced by means of a reservoir which allows emptying of the balloon when the urethral pressure exceeds the reservoir pressure. Measurements were performed in the high pressure zone in a 55-year-old continent women. Paper speed 15 mm/s. (B) Measurement of CA pressure changes during squeezing and coughing at the bladder neck in the same woman.

variation into variation between subjects, variation between sites of measurement and random variation. The normal range of power was determined as the 95% interval (mean $\pm$ 2 SD of log data).

All computations were made on an IBM PC XT computer using the statpackage Minitab.

Data recording equipment

CA, P_{ura} , P_{ves} and EMG were recorded, processed and displayed on a 6-channel recording system (DISA UROsystem 21F 16 2100). The frequency response of the amplifying system was 100 Hz and

the paper speed was 15 mm/s. EMG activity was recorded in the range 4–10 μ V/Div.

Results

The urethral pressure at rest and the pressure increase (ΔP_{ura}) during coughing and squeezing at the 3 sites of measurement are shown in Table 1. Three women had equalisation of pressure between the bladder neck site and the bladder during coughing. A statistically significant difference between the mean pressures at the 3 sites was found

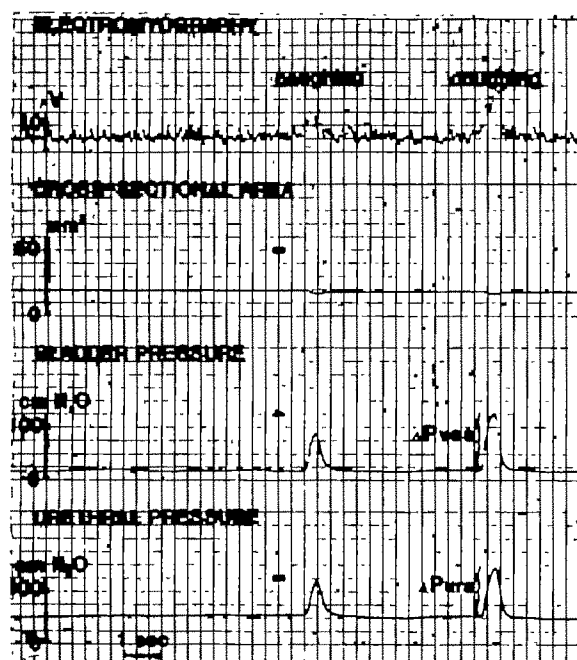


Fig. 4 Simultaneous recording of urethral and bladder pressure at rest and during coughing at a fixed CA of approximately 20 mm² of the balloon. Measurements were performed in the urethral high pressure zone. ΔP_{ure} and ΔP_{vsa} indicate the pressure increase in the urethra and in the bladder respectively during coughing. Paper speed 15 mm/s.

for all 3 variables ($P < 0.01$). At each site the pressure increase during coughing was significantly greater than the increase during squeezing. The mean bladder pressure at rest was 22 cm H₂O (range 8–57) and the mean bladder pressure increase (ΔP_{vsa}) during squeezing was 6 cm H₂O (range –15–55). A significant positive correlation between the urethral pressure generation during coughing and squeezing in the individual subject was found

Table 1 Measurement of Urethral Pressure (means $\pm$ SD)

	At rest P_{ure}	Pressure increase		Coughing versus squeezing
		ΔP_{ure} (coughing)	ΔP_{ure} (squeezing)	
Bladder neck	60 $\pm$ 26	65 $\pm$ 29 (66 $\pm$ 28)*	30 $\pm$ 17	$P < 0.0001$
Midurethra	71 $\pm$ 23	73 $\pm$ 34	24 $\pm$ 16	$P < 0.0001$
Distal urethra	35 $\pm$ 16	39 $\pm$ 29	16 $\pm$ 10	$P < 0.005$

ANOVA showed significant variation between the 3 sites of measurement for all 3 variables ($P < 0.01$). *The 3 women with equalisation of pressure between the bladder neck and the bladder have been excluded

Table 2 Generation of Urethral Power

	Urethral power (mWatt; joule/s $\times 10^3$)		P
	Coughing	Squeezing	
Bladder neck	10.1 (29.5–3.4)	4.7 (15.2–1.5)	< 0.0001
Midurethra	11.8 (37.5–3.7)	4.0 (23.2–0.7)	< 0.0001
Distal urethra	6.5 (21.6–2.0)	2.4 (15.9–0.4)	< 0.0001

Values are means and 95% interval (mean $\pm$ 2 SD of log data) in parenthesis.

at the bladder neck ($r = 0.58$, $P < 0.01$) and midurethrally ($r = 0.41$, $P < 0.05$) but not distally in the urethra ($r = 0.26$, ns).

The urethral power generated during coughing and contraction of the pelvic floor at different sites in the urethra are listed in Table 2. The power created during coughing was statistically greater ($P < 0.0001$) than the power generated during squeezing along the whole length of the urethra. During coughing and squeezing respectively the median power generation was essentially the same midurethrally and at the bladder neck. The inter-individual variation and the variation related to the site of measurement were statistically significant during both procedures ($P < 0.05$ and $P < 0.01$ respectively). The minimum power was measured distally in the urethra during both procedures. A significant positive correlation was found between the power generated during coughing and during squeezing at the bladder neck ($r = 0.42$, $P < 0.05$), midurethrally ($r = 0.55$, $P < 0.01$) and distally in the urethra ($r = 0.40$, $P < 0.03$).

No significant correlation was established between the power created during coughing or squeezing and age or parity. A weak, non-significant negative correlation was found between the power created in the high pressure zone during both procedures and parity.

Discussion

The method used in this study made it possible to describe quantitatively the adjunctive occlusive forces of the female urethra, in the physical term of power. Pressure increase and power could be compared at different segments of the urethra during coughing and voluntary contraction of the pelvic floor. It was found that the maximum values of pressure increase and power were generated at the bladder neck during voluntary contraction

despite the fact that the resting pressure was maximum midurethrally. The pressure increase during squeezing cannot be explained by an accompanying increase in intra-abdominal pressure, since the bladder pressure increase was much less and actually decreased in several women during this manoeuvre. We therefore suggest that the power and pressure generation during squeezing is caused by an active mechanism which provides the bladder neck with strong dynamic properties. This may be explained anatomically by the attachment of the anterior vaginal wall to muscles of the pelvic diaphragm and to the arcus tendineus of the pelvic fascia (White, 1912; Richardson *et al.*, 1981; De Lancey, 1986, 1989). This fibromuscular sling structure is said to be located in the proximal part of the urethra from the 20th to the 60th percentile of the urethra (De Lancey, 1986), which corresponds to the proximal sites of measurement used in this study. It is therefore suggested that power generation at the bladder neck, during both squeezing and at least partly during coughing, is due to activation of this vagino-levator sling system with compression of the urethral lumen. This is consistent with previous reports by Muellner (1951) and Jeffcoate and Roberts (1952), who claimed that the proximal urethra and bladder neck are mobile and their position is under voluntary control. This concept is substantiated by more recent measurements. Colstrup (1985) observed a strong dynamic closure force at the bladder neck and Constantinou (1985) noted that the urethral force measured with a microtip transducer was greatest posteriorly in the proximal urethra and anteriorly in the distal portion. This indicates that an extrinsic structure affects the proximal part of the urethra. Although the striated urethral sphincter with circular fibres is partly located in the proximal part of the urethra (DeLancey, 1986), the strong dynamic muscle action cannot be caused either by this tiny slow twitch muscle coat (Huisman, 1983) or by smooth muscles. During coughing, experimental and clinical data suggest that both active and passive mechanisms collaborate to augment the urethral closure forces (Heidler *et al.*, 1979; Constantinou, 1982; Thüroff *et al.*, 1982; Van der Kooi *et al.*, 1984). It has been established that passive transmission is most active at the bladder neck and fades gradually distally in the urethra (Obrink *et al.*, 1978). However, proof of the significance of passive pressure transmission in the maintenance of continence in the female is lacking, since it has been difficult to separate active and passive pressure generation.

During coughing the pressure increase and power generation were greatest midurethrally indicating that active mechanisms are involved. This is supported by the correlation between pressure generation during squeezing and coughing in the individual woman. These results are in accord with animal experiments showing that passive transmission is of minor importance compared to the active component for pressure generation during coughing (Heidler *et al.*, 1987; Thüroff *et al.*, 1987). However, one cannot exclude the possibility that mechanical mechanisms such as urethral kinking (Beck *et al.*, 1988) and/or compression of the proximal urethra against the symphysis pubis (Hertogs and Stanton, 1982) are involved in pressure generation during coughing.

The present methodology involves the proximal microtip transducer being inside a water-filled balloon. This should provide more valid pressure data than conventional microtip transducer techniques, since artefacts caused by directional variations are eliminated (Van der Kooi *et al.*, 1988). The reproducibility of measurement of urethral power has been reported to be of the order ± 3 mWatt, which seems clinically acceptable (Lose and Schroeder, 1990). There seems to be a close association between the mean power and mean pressure generation during coughing and squeezing, although in the individual woman the 2 parameters did not always vary in parallel. Thus we believe that power (joule/s) is the preferred parameter since it includes the dimension of time and hence better describes the dynamic event itself.

This study has provided new quantitative data concerning the occlusive forces along the urethra and demonstrates the presence of a strong active mechanism both at the bladder neck and in the midurethra during coughing and squeezing. The results also indicate that the strong dynamic sphincter function of the bladder neck is due to the vagino-levator fibromuscular sling structure. However, a single sling system would be unable to generate sufficient power unless it was counterbalanced by another mechanism *e.g.* another sling. Our data are therefore consistent with the concept that such a double sling system is present at the bladder neck (Olesen and Grau, 1976; De Lancey, 1988).

Acknowledgement

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Urethral Pressure and Power Generation during Coughing and Voluntary Contraction of the Pelvic Floor in Females with Genuine Stress Incontinence

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Summary—A probe which permits continuous measurement of the related values of pressure and cross-sectional area in the female urethra was used for a quantitative description of the adjunctive closure forces in terms of pressure and power generation during coughing and squeezing in 30 females with genuine stress incontinence (GSI). Measurements were performed at the bladder neck, midurethrally and distally in the urethra.

A statistically significant decrease in power generation was found at the bladder neck and midurethrally during squeezing compared with the values in healthy females. During coughing the power generation was significantly decreased midurethrally and measurement of pressure generation revealed similar results. These findings indicate that the active closure mechanisms at the bladder neck and midurethra are significantly weakened in females with GSI. The results do not support the concept that impaired passive pressure transmission to the urethra is an important pathophysiological factor in GSI.

Genuine stress incontinence occurs when collaboration between the permanent and the adjunctive closure forces of the urethra cannot prevent leakage during stress episodes (in the absence of detrusor activity).

It has been shown that the permanent closure forces are weakened along the length of the urethra, particularly at the bladder neck, in females with GSI (Lose, 1989; Lose and Colstrup, 1990). However, factors other than those related to the static state of the resting urethra seem to be involved in the pathophysiology of GSI (Lose, 1989; Lose and Colstrup, 1990). This is consistent with the generally accepted theory that the dynamic (adjunctive) closure forces are defective in patients with GSI either because of decreased passive pressure transmission from the abdomen to the urethra or active pressure generation due to impaired function of the striated muscles in and around the urethra (Enhörning, 1961).

A method has been developed which allows direct quantitative measurement of the urethral occlusive forces in terms of power generated during coughing and voluntary contraction of the pelvic floor (Lose *et al.*, 1988a; Lose and Colstrup, 1990, 1991). The aim of this study was to determine the urethral pressure and power generation during coughing and voluntary contraction of the pelvic floor in females with GSI and compare the results with those obtained in healthy women.

Patients and Methods

Thirty women referred consecutively with GSI were studied. All had pure stress incontinence and urine leakage. The median age was 49 years (range 37–76); 17 were pre-menopausal and 13 were post-menopausal. The median parity was 2.5 (range 0–4). None had undergone surgery for incontinence. Five had undergone hysterectomy but this had not affected the incontinence that was present before surgery.

Examination consisted of a detailed history, urine culture, pad weighing test, pelvic examination, cystoscopy, stress test, uroflowmetry, sitting cystometry, urethral pressure profilometry, pressure flow study, voiding colpocysto-urethrography (VCU). Measurement of the urethral pressure and power generation during coughing and squeezing was performed using a specially designed probe (Lose *et al.*, 1988a; Lose and Colstrup, 1991).

All patients underwent a 1-h pad weighing test according to the modification described by Lose *et al.* (1988b). If this test was negative, a 24-h home pad weighing test was carried out (Jørgensen *et al.*, 1987). A positive result with at least 1 of the 2 pad weighing tests was a prerequisite for entering the study. The stress test was performed with the patient in the standing position with 200–300 ml saline in the bladder. The patient was asked to cough repeatedly. The test was considered positive if objective leakage was observed. Urethral pressure profilometry was carried out according to the technique described by Brown and Wickham (1969). An 8 F single lumen catheter with 2 side-holes 5 cm from the tip was used for recording the urethral pressure in a lateral orientation at a withdrawal speed of 3 mm/s and a perfusion rate of 2 ml/s. Cystometry and a pressure flow study of micturition were performed according to Lose *et al.* (1986). Voiding colpocysto-urethrography and the classification of bladder suspension defects were made according to Olesen (1983).

Recording of urethral pressure and power generation was performed with a specially designed probe which measures the related values of pressure and cross-sectional area in the urethra. This method allows calculation of power ($= \text{pressure} \times \text{volume displaced} \times \text{s}^{-1}$) during coughing and squeezing (Lose *et al.*, 1988a). The patients were investigated in the supine position with an empty bladder as described for healthy women (Lose and Colstrup, 1991). Measurements were performed (a) at the bladder neck (0.75 cm from the urethrovesical junction), (b) midurethrally (in the high pressure zone) and (c) distally in the urethra (0.75 cm from the external meatus). At each position the following procedure was carried out. After induction of a CA of approximately 50 mm² each patient was asked to cough and then to squeeze (hold urine) 3 times. The most vigorous cough and squeeze was used to calculate the power of contraction. During these manoeuvres the related values of CA and pressure (P_{ura}) were registered with the balloon open to a reservoir to allow for emptying of the balloon (Fig. 1). P_{ura} at rest and the pressure increase (ΔP_{ura})

during coughing and squeezing were measured at a fixed CA of approximately 20 mm² (Fig. 2). During coughing and squeezing the catheter was fixed manually at the external urethral orifice. All measurements were performed by the author. The work (W) produced by the urethra to deflate the balloon is the volume reduction dV of the balloon multiplied by the maximum pressure in the balloon (P_{ura}), i.e. $W = P_{\text{ura}} \times dV$. If the balloon is considered to be cylindrical, with a length of 0.01 m, the volume can be expressed as $CA \times 0.01$ (m³). The work produced by voluntary contraction of a cylindrical segment with the length of 0.01 m with uniform properties would be $W = P_{\text{ura}} \times dCA \times 0.01$ (kPa $\times$ m² $\times$ m = joule; 1 kPa = 10 cm H₂O). Since the duration of work can be read from the tracing, the power (joule/s = watt) of the contraction can be calculated.

GSI was diagnosed in one of the following ways: (1) observation of leakage produced by stress without evidence of detrusor activity during urodynamic testing (26 patients); (2) a positive pad weighing test in the absence of detrusor instability on cystometry or significant residual urine (4 patients). Informed consent was obtained from all patients and the study was approved by the regional Scientific Ethical Committee.

Methods, definitions and units of measurement conform to the standards proposed by the International Continence Society except when specifically stated.

Data recording equipment

CA, P_{ura} , P_{ves} and electromyography (EMG) were recorded, processed and displayed on a 6-channel recording system (DISA UROsystem 21F 16 2100). The frequency response of the amplifying system was 100 Hz. The paper speed was 15 mm/s. EMG activity was recorded in the range 4–10 $\mu\text{V}/\text{Div}$.

Statistical methods

Statistical analysis was based on standard parametric methods (Diem and Lentner, 1975). Urethral pressure was found to follow a normal distribution while power did not. However, after logarithmic transformation, normality was obtained for power data. Differences between the 3 sites of measurement were tested using analysis of variance (ANOVA). This allowed separation of the total variation into variation between subjects, variation between sites of measurement and random variation. The ranges of power data were determined as the 95% interval (mean $\pm$ 2 SD of log data). All computa-

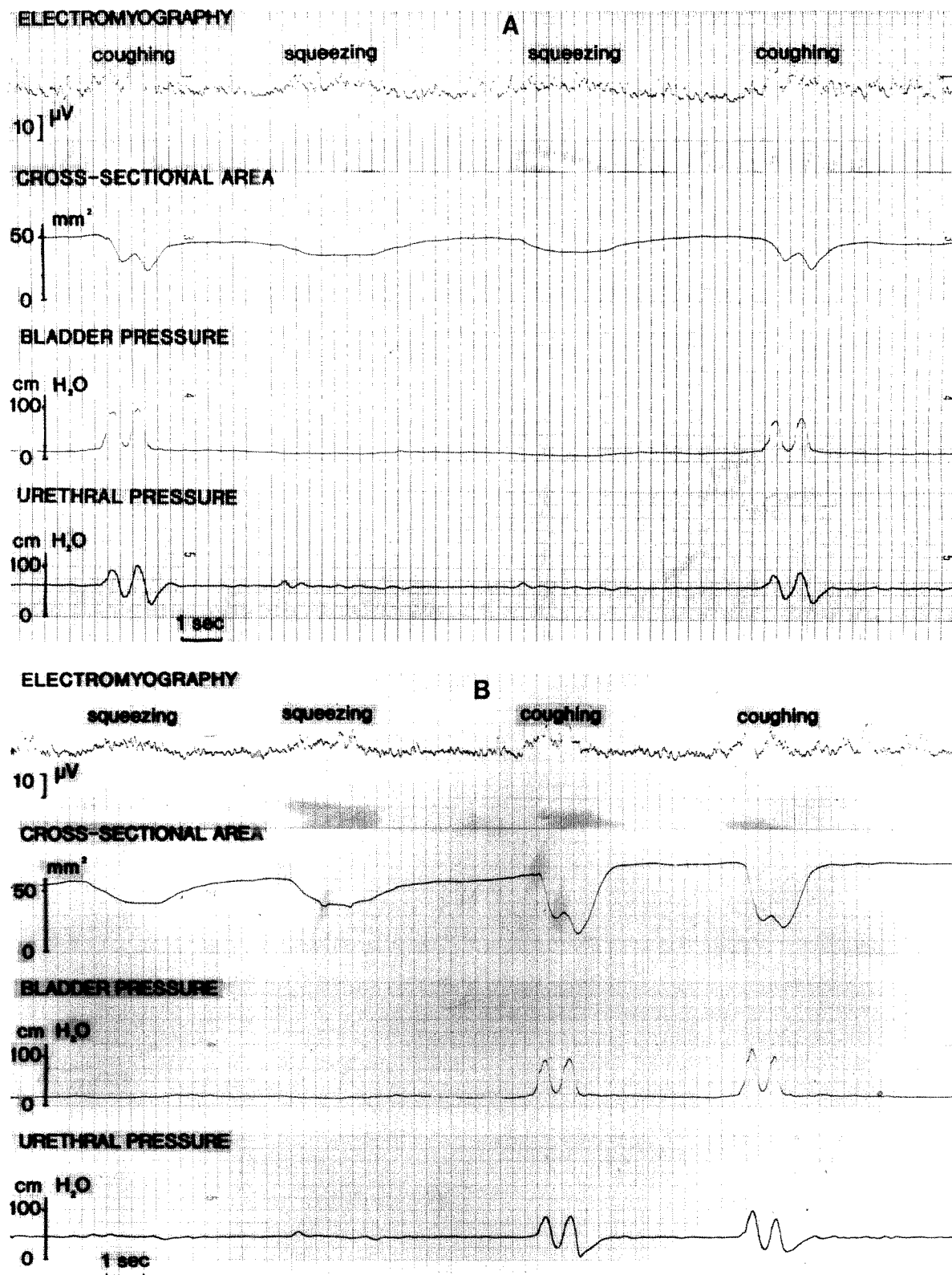


Fig. 1 (A) Measurement of cross-sectional area (CA) in the urethra of a stress incontinent woman after induction of a constant pressure of 50 cm H_2O and the CA-pressure changes during squeezing and coughing. The pressure was induced by means of a reservoir which allows emptying of the balloon against an almost fixed pressure. Measurements were performed in the high pressure zone. Paper speed 15 mm/s. (B) Measurement of CA-pressure changes during squeezing and coughing at the bladder neck in the

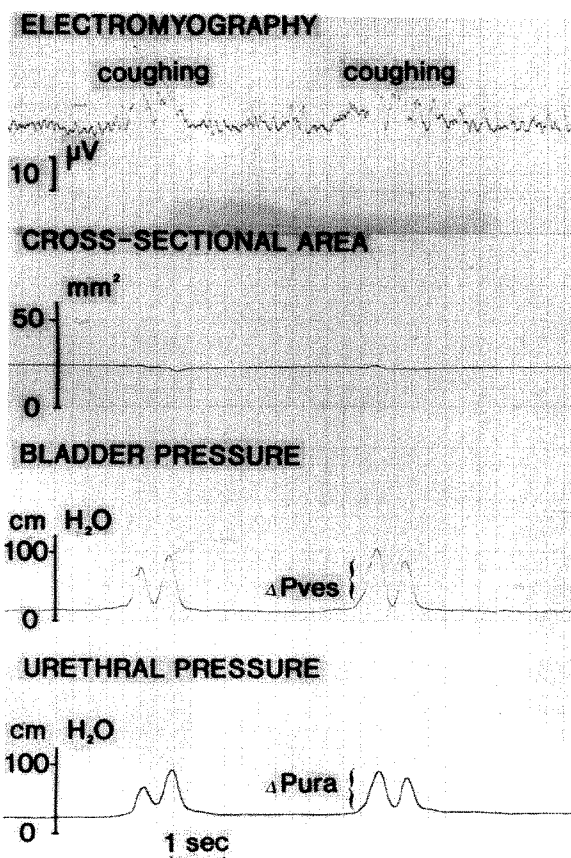


Fig. 2 Simultaneous recording of urethral and bladder pressures at rest and during coughing at a fixed CA of approximately 20 mm² of the balloon. Measurements were performed in the urethral high pressure zone. ΔP_{ura} and ΔP_{ves} indicate the pressure increase in the urethra and bladder respectively during coughing. Paper speed 15 mm/s.

tions were made on an IBM PC XT computer using the statpackage Minitab.

Results

The median urine loss during the 1-h pad weighing test was 9 g (range 0–77). In 6 patients this test was

negative, but significant leakage (>8 g/24 h) was demonstrated during the 24-h test. The stress test was positive in 23 patients. At VCU 13 patients had an anterior, 5 a posterior and 2 a combined anterior and posterior bladder suspension defect. Five VCUs were normal and 5 patients were not subjected to this examination. The median functional profile length was 33 mm (range 21–43). Eight patients had a cystocele at gynaecological examination.

The urethral pressure at rest and the pressure increase (ΔP_{ura}) during coughing and squeezing at the 3 sites of measurement are shown in Table 1. Sixteen patients had equalisation of pressure between the bladder neck and bladder during coughing. A statistically significant difference in mean urethral pressure at the 3 sites of measurement was found for all 3 parameters ($P < 0.01$). At each site of measurement the pressure increase during coughing was significantly greater than the increase during squeezing. The mean bladder pressure at rest was 19 cm H₂O (range 8–57) and the mean bladder pressure increase (ΔP_{ves}) during squeezing was 6 cm H₂O (range –10–15).

No significant correlation between generation of urethral pressure during coughing and squeezing in the individual woman could be obtained. Urethral power generation during coughing and contraction of the pelvic floor at different sites in the urethra is shown in Table 2. Power generation during coughing was statistically greater ($P < 0.0001$) than the power generated during squeezing along the entire length of the urethra. During both coughing and squeezing the power generation was greatest at the bladder neck. A significant inter-individual variation in the power generated was found during both procedures. The difference in power generation at the 3 sites of measurement was statistically significant ($P < 0.01$) during coughing, while during squeezing it was not significantly different. The minimum power was measured distally in the urethra during both procedures. A statistically significant positive correlation was found between

Table 1 Measurement of Urethral Pressure (mean $\pm$ SD) in 30 Women with Genuine Stress Incontinence

	Pressure increase			Coughing versus squeezing
	At rest P_{ura}	ΔP_{ura} (coughing)	ΔP_{ura} (squeezing)	
Bladder neck	35 $\pm$ 12	60 $\pm$ 26 (49 $\pm$ 22)*	17 $\pm$ 9	$P < 0.005$
Midurethra	44 $\pm$ 13	49 $\pm$ 22	16 $\pm$ 10	$P < 0.005$
Distal urethra	28 $\pm$ 15	35 $\pm$ 20	9 $\pm$ 7	$P < 0.005$

ANOVA showed significant variation between the 3 sites of measurement for all 3 variables ($P < 0.01$). * The 16 patients with pressure equalisation between the bladder neck and bladder were excluded.

Table 2 Power in mWatt (joule/s $\times 10^3$) Generated at Different Sites in the Urethra in 30 Women with GSI

	Urethral power		<i>P</i>
	Coughing	Squeezing	
Bladder neck	8.4 (19.6–3.6)	2.3 (8.6–0.6)	<0.0001
Midurethra	7.2 (24.2–2.1)	2.0 (10.4–0.4)	<0.0001
Distal urethra	5.0 (15.1–1.7)	1.6 (7.3–0.3)	<0.0001

Values are means and 95% interval (mean $\pm$ 2 SD of log data) in parenthesis.

power generation during coughing and squeezing midurethrally ($r=0.70$, $P<0.001$) but no correlation was obtained at the bladder neck ($r=0.24$) and distally in the urethra ($r=0.07$).

There was no statistically significant correlation between the power created during coughing or squeezing and age or parity.

In Table 3 the significance of differences between levels of power generation in GSI patients and normals is compared.

Discussion

This study has revealed a statistically significant decrease in power generation in the midurethra during coughing and squeezing in patients with GSI. This seems to indicate impaired function of the striated urethral sphincter and/or the pelvic floor muscles and is consistent with recent electrophysiological studies which have shown partial denervation of the pelvic floor in patients with GSI (Anderson, 1984; Snooks *et al.*, 1985; Smith *et al.*, 1989a, 1989b). However, other pathophysiological factors may contribute to the decreased active power generation, *viz.* changes in the mechanical properties of fascia and ligaments around the urethra (Ulmsten *et al.*, 1987; Landon *et al.*, 1988)

Table 3 Statistical Significance of Differences between Mean Levels of Power Generation in 30 Normal Women and 30 Women with GSI

	Urethral location		
	Bladder neck	Midurethra	Distal urethra
Squeezing	0.0001	0.003	ns
Coughing	ns	0.002	ns

Level of significance $P<0.01$.

and/or increased elastance of the urethral wall due to fibrosis (Zinner *et al.*, 1976; Lose, 1989).

It has been shown that the proximal part of the urethra is influenced by a strong active voluntary closure mechanism (Colstrup, 1985; Lose and Colstrup, 1991), probably caused by the vaginolevator sling system described by DeLancey (1989). The present data demonstrate that this closure mechanism is significantly weakened in patients with GSI. This may indicate that the function of the sling system is impaired, which could be due to weakening of either the pubourethral ligaments, their attachment or the levator in which the ligaments are anchored.

Generation of power at the bladder neck during coughing was also found to be reduced in patients with GSI, although not to a statistically significant degree. This would indicate that factors other than active mechanisms contribute to the pressure/power generation at the bladder neck during coughing. This is in accordance with the concept that passive closure mechanisms due to pressure transmission (Enhörning, 1961) or mechanical mechanisms (Beck *et al.*, 1988) contribute to closure of the bladder neck during stress episodes.

It has been suggested that defective passive pressure transmission from the abdomen to the urethra during stress may be a pathophysiological factor in GSI (Enhörning, 1961). The present data show that the mean active (squeeze) power generation was reduced by approximately 50% along the urethra in patients with GSI, while the mean power generation during coughing, which expresses both passive and active mechanisms, was reduced by only 25% and less pronounced at the bladder neck. Since passive transmission has been shown to work primarily at the bladder neck (Obrink *et al.*, 1978; Obrink and Bunne, 1978; Constantinou, 1982), the present data do not support the theory of defective passive pressure transmission as an important factor in GSI, but they are in agreement with the study of Bunne and Obrink (1978). Similarly, they seem to contradict the concept that mechanical mechanisms at the bladder neck are impaired in GSI.

Significant inter-individual variation in power generation was found in both normal women (Lose and Colstrup, 1991) and those with GSI. Together with a considerable overlap between the values obtained in the 2 groups, this indicates that factors other than the adjunctive closure forces are involved in the pathogenesis of GSI. This is in agreement with previous studies showing that the static mechanical properties are weakened in these

women (Lose, 1989; Lose and Colstrup, 1990). The results of this study support the concept that GSI is due to impaired bladder neck function combined with defective urethral sphincter and/or pelvic floor function.

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Assessment of the Long-term Results of Subtrigonal Phenolisation

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Summary—Long-term follow-up was conducted on 97 patients who had undergone subtrigonal phenolisation for detrusor instability, bladder hypersensitivity, detrusor hyper-reflexia or interstitial cystitis. The procedure failed to alleviate lower urinary tract dysfunction in 57% of patients; it had an unsustained benefit in 24% and long-term success was experienced by only 19%. It was most effective in the hypersensitive bladder of unknown cause. The incidence of complications (17%) suggests that the procedure should only be undertaken if more invasive measures are the only available alternative, and the possibility of these complications should be explained to the patient.

Subtrigonal phenolisation has been employed since 1982 in the treatment of patients with detrusor instability, hyper-reflexia and bladder hypersensitivity who are resistant to more conservative measures. Its appeal lay in providing a simple, minimally invasive procedure for patients who would previously have been subjected to a more major surgical procedure—sacral neurectomy, sub-hypogastric ganglion transection or bladder transection. Injection of local anaesthetic into the subtrigonal region gave encouraging results and was replaced by aqueous phenol with a reported success rate of 76% in females with detrusor instability or hyper-reflexia (Ewing *et al.*, 1982).

Most initial reports suggested that the technique was effective in the management of the older patient with detrusor instability and particularly in patients with detrusor hyper-reflexia (Blackford *et al.*, 1984; Cameron-Strange and Millard, 1988). It has fallen out of favour recently because some reports have suggested that initial optimism regarding the efficacy of the techniques has been misplaced (Rosenbaum *et al.*, 1990) and that side effects may be more common and more severe than previously suspected.

In view of the discrepancy in reported success rates we have reviewed our long-term success rate.

Patients and Methods

Between 1982 and 1987, 97 patients underwent transvesical phenolisation. Complete data have been obtained on 72. There were 9 males and 63 females with a mean age of 49 years (range 9–78). All patients had undergone pre-operative urodynamic tests and indications included detrusor instability, detrusor hyper-reflexia, bladder hypersensitivity and interstitial cystitis.

All but 5 patients had 10 ml of 6% aqueous phenol injected under general anaesthesia through a 35 cm 20 gauge Shuttleworth needle via a cystoscope under direct vision. The needle was inserted below and lateral to the ureteric orifice on the trigone so that the top of the needle was finally positioned behind the intramural ureter in the area of the pelvic plexuses.

Bilateral injections were performed except in 2 patients who had each side treated on separate occasions. A second phenolisation procedure was performed in 7 patients and 5 patients had only 5 ml injected bilaterally.

Follow-up included urine culture, videourodynamics and intravenous urography. The maximum

follow-up period was 7 years and the minimum 3 years. Substantial improvement in the patient's pre-operative symptoms was termed a "success".

Results

Overall, 14 patients (19%) have shown long-term improvement. Unsustained improvement from 1 week to 3 years was seen in 17 (24%) and 41 (57%) were unchanged by phenolisation. The results for the various subgroups are enumerated in the Table, which shows that the procedure was of long-term value only in patients with hypersensitive bladders of unknown cause; in them the long-term success rate was 28%, though a further 31% had symptomatic relief for a variable period.

Table Results of Treatment

Group	No.	Short-term Improvement	Long-term Improvement
Hypersensitive	29	9	8
Detrusor instability	26	5	3
Poor compliance	8	1	2
Interstitial cystitis	5	2	0
Multiple sclerosis	4	0	1
Total	72	17	14

A significant complication rate (17% overall) accompanied the procedure. The commonest complication, persistent urinary retention, occurred in 8 patients; 1 of these was transient. The others required intermittent self-catheterisation. Four nerve palsies were seen. Two were sciatic; 1 of these was transient but the other persisted; 1 obturator nerve palsy was seen and 1 patient developed a discrete area of paraesthesia and numbness which failed to resolve. Two patients developed localised bladder mucosal necrosis at the injection site and stone formation ensued in 1 case. Erectile impotence developed in 1 of the 9 male patients. He had been warned of the possibility pre-operatively and had a good result from phenolisation. None of the other males derived any benefit from the procedure.

Other series have reported fistula formation (Wall and Stanton, 1989) but no fistulas were encountered in this series, and undoubtedly this complication arises from placing the phenol too medially.

In those patients who either failed to respond to phenolisation or developed complications afterwards, 17 (24% overall) underwent a subsequent operative procedure for their lower urinary tract

dysfunction. The commonest procedure was the clam ileocystoplasty (11 patients).

Discussion

The efficacy of aqueous phenol as a neurolytic agent is not in doubt (Parkhouse *et al.*, 1987), but prolonged follow-up in this series reveals that, although there was an initial improvement rate of 43%, the overall long-term success rate was only 19%. The original indication in the series of Ewing *et al.* (1982) was hyper-reflexia and the best results in our series in 1984 (Blackford *et al.*) were also in the neuropathic group, but most of the patients with hyper-reflexia were treated in the unit at Guy's Hospital, London, and almost all of the hypersensitive group were Cardiff-based. All but 1 of these were females with the urge syndrome, stable bladders, discomfort on filling and generally reduced capacity. This remains the most difficult and recalcitrant "minor" disturbance of bladder behaviour to treat. Our neuropathic population is too small to comment on, but other workers continue to use the technique. In our judgement, phenolisation is an acceptable treatment in selected neuropathic bladders and in patients with severe intractable hypersensitivity of unknown cause.

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Bladder Substitution with Ileocaecal (Mainz) Pouch Clinical Performance over 2 Years

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Summary—A series of 11 patients underwent ileocaecal bladder substitution (Mainz pouch) with urethral anastomosis after radical cystectomy and pelvic lymphadenectomy for moderate to high grade transitional cell carcinoma of the bladder.

With 12 to 27 months of follow-up (mean 18), 6 patients are voiding and are dry day and night with timed voidings; 4 patients continue intermittent catheterisation because of inability to perform the Valsalva manoeuvre adequately, and 1 has a suprapubic tube because of stricture of the enterourethral anastomosis.

Upper tract studies revealed dilatation of 4 of 22 renal units and 1 patient required endourological intervention. Serum electrolyte studies revealed slightly elevated chloride levels in 6, mild hypocarbia in 3, and reduced vitamin B₁₂ levels in all patients, but no megaloblastic anaemia. The Mainz pouch appears to have very satisfactory short- and intermediate-term results.

The last 5 years have seen a tremendous resurgence of interest in the use of bowel segments as bladder substitutes. Ideally, a bladder substitute should have an adequate capacity with antirefluxing non-obstructing ureteric anastomoses, the ability to empty completely, and continence with either an abdominal stoma or anastomosis to the urethra. The choice of bowel segment is influenced by the physical characteristics of bowel, the technical simplicity of pouch construction and the extent of metabolic sequelae. The final consideration depends on the results of long-term follow-up with assessment of complication rates.

This report details our initial experience with the detubularised ileocaecal segment with anastomosis to the urethra. The Mainz pouch, as originally described by Thuroff and Hohenfellner (1986), has been used in an attempt to create continent urinary reservoirs for 11 men.

Patients and Methods

Between April 1986 and June 1987, 11 men aged 51 to 75 years (average 61) underwent bladder substitution with the ileocaecal segment after pelvic lymphadenectomy and radical cystoprostatectomy for moderate to high grade transitional cell carcinoma (with associated carcinoma *in situ* in 4 cases). Only 1 patient had a documented history of progression from superficial bladder cancer. All patients were free of metastatic disease on pre-operative evaluation, although 2 proved to have microscopic nodal disease. Four patients were found on pathological examination to have coexistent prostatic carcinoma, which had been suspected in only 1 case, and 1 of these also had transitional cell carcinoma invasive to the prostatic ducts not revealed by pre-operative transurethral biopsy. All patients had tumour-free margins on intra-operative frozen section and final pathological review.

All patients had an oral mechanical bowel preparation with Colyte (colon electrolyte lavage preparation; Reed and Carnrick, Piscataway,

USA) while on a 48-h clear liquid diet. A parenteral first-generation cephalosporin was used in the peri-operative period and each patient received prophylaxis with either pneumatic compression stockings or sodium warfarin to prevent deep vein thrombosis.

Technique

The patient was placed in a modified lithotomy position, allowing a surgical assistant to apply perineal pressure when necessary during fixation of the enterourethral anastomosis (Lange and Reddy, 1987). Before cystectomy, 10% formalin was instilled into the bladder for 10 min.

Pouches were constructed as described by Thuroff and Hohenfellner (1986) from 10 to 15 cm of caecum and ascending colon and 2 contiguous 10- to 15-cm segments of terminal ileum. The essential features of the operation are detubularisation and reconfiguration of the bowel by incision and reanastomosis along the antimesenteric borders (Fig. 1). The ureters were implanted into the caecum by submucosal tunnels and stented with 90-cm 7F Silastic stents (Surgitek). The pouch was drained by two 20F Silastic Foley catheters, 1 suprapubic and 1 urethral. Two Penrose drains were placed adjacent to the pouch. Pouch construction and cystectomy were performed by a single surgical team.

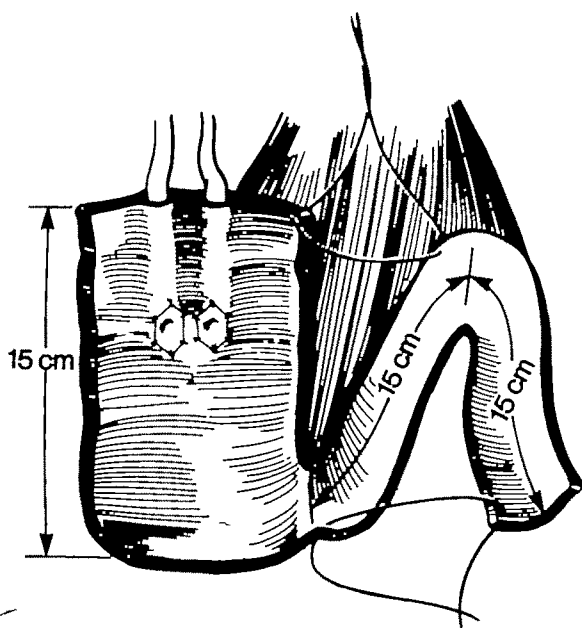


Fig. 1 Schematic diagram demonstrating segments of large and small bowel required for construction of the ileocaecal bladder substitute (Mainz pouch).

Ureteric stents were removed after the patients had been on a normal diet for a minimum of 2 to 3 days. Stents were removed one at a time to permit differential pouch and ureteric urine collection. All patients received pouch irrigations with sterile saline every 6 to 8 h as long as the suprapubic tubes remained. Pericatheterograms were obtained at 10 days, and repeated weekly if extravasation occurred. Urethral catheters were removed between 2 and 3 weeks post-operatively. The suprapubic tubes were removed after an additional 2 weeks when satisfactory voiding was established. Patients were maintained on once-daily suppressive antibiotics for 4 to 6 weeks post-operatively. All were taught clean intermittent catheterisation techniques as a safeguard against anastomotic obstruction by mucus.

Three patients received adjuvant chemotherapy with the Northern California Oncology Group regimen of cisplatin, methotrexate and vinblastine (Table 1) (Harker *et al.*, 1985). In 1 patient chemotherapy was instituted for anaplastic Stage T3B disease and in 2 for microscopic pelvic nodal metastases.

Follow-up

All patients had intravenous urograms (IVU) 4 to 6 weeks post-operatively and then every 4 to 6 months. Metabolic assessment included peri-operative urinary and serum electrolytes. Serum levels of vitamin B₁₂, folate, magnesium and urea nitrogen (BUN) and red cell indices were also measured. Patients underwent urodynamic studies pre-operatively, 6 weeks after the operation and quarterly thereafter. Pull-through urethral pressure profiles and water cystometry at 27°C were performed with a 7F 3-channel membrane transducer with a 5F lumen at 50–75 ml/min inflow rates. Recordings were made by a polygraph of UCSF Medical Center design or a modified DISA/Dantek Uroflow System.

Results

Pouch construction, re-establishment of bowel continuity and creation of the enterourethrostomy added a mean of 4½ h (range 3–7) to the standard radical cystectomy. The mean operative blood loss was 3 units (range 2–5). All patients resumed normal diets between 7 and 10 days post-operatively. None had prolonged diarrhoea and no instance of deep vein thrombosis was noted. The enterourethral anastomoses healed in 9 of 11 patients between 2 and 3 weeks post-operatively.

Table 1 Details of Patients

Patient no.	Age (years)	Tumour grade	TNM classification bladder, prostate	Follow-up (months)	Comments
1	51	TCCB III	pT3aN2M0	22	Continent, nocturia $\times 2$ (CMV)
2	60	TCCB III/IV, Cis AdenoCaP Gleason 3/3	pT4N0M0 pT2bN0M0, Gleason 3/4	17	Continent, nocturia $\times 1$
3	63	TCCB III/IV	pT3bN0M0	23	Continent, ISC
4	59	TCCB IV	pT2N0M0 pT29N0M0, Gleason 2/2	16	Continent, nocturia $\times 1$
5	75	TCCB, Cis	pTISN0M0 pT3N0M0, Gleason 3/3 (Caecal Ca, Duke's B)	19	Suprapubic tube
6	55	TCCB III/IV	pT1N0M0, Tis	27	Continent, nocturia $\times 2$
7	63	TCCB III/IV	pT3bN0M0 anaplastic	19	Continent, ISC (CMV)*
8	65	TCCB II/III	pT3bN1M0	12	Nocturia $\times 2$ (CMV)
9	52	TCCB III	pT3bN0M0	25	Continent, nocturia $\times 2$
10	75	TCCB, Cis	pT2N0M0, Tis pT1N0M0, Gleason 1/2	14	Continent day, ISC, enuresis
11	54	TCCB, Cis	pT1N0M0, Tis	17	Continent, ISC

ISC: Intermittent self-catheterisation regimen.

* Pulmonary metastasis at 9 months.

Enuresis: Nocturia $> \times 2$ or use of > 1 pad at HS.

CMV: Cisplatin, methotrexate, vinblastine.

Two patients required 4 and 6 weeks to heal completely.

Six patients are voiding and are dry at night with 1 or 2 night voidings at 4-h intervals (Table 1). All of these patients are continent during the day and avoid nocturnal incontinence by timed voidings. The post-void residual volume is less than 50 ml. Patients perform the Valsalva manoeuvre to void, and several have adopted the seated position to maximise abdominal pressure, to facilitate the Credé manoeuvre and to avoid soiling from inadvertent faecal loss.

Four patients remain on intermittent self-catheterisation because of an inability to perform the Valsalva manoeuvre adequately and to relax the perineal muscles simultaneously. One patient has a suprapubic tube as a result of anastomotic complications.

Radiography

Four of the 22 renal units showed dilatation, but only 1 patient required endourological intervention with uretero-enteral balloon dilatation and stenting. This patient developed renal failure after cisplatin-based chemotherapy and left ureteric obstruction requiring emergency placement of a percutaneous nephrostomy tube followed by antegrade stenting.

Metabolic studies

Urinary samples were collected from indwelling ureteric stents and suprapubic tubes in 3 patients. The patients were on oral alimentation without intravenous supplements. Figure 2 summarises the mean values of urinary sodium, potassium, chloride and osmolality over 9 patient days. There was clear evidence of Na, Cl and K absorption from pouch urine with a consequent decrease in osmolality (the mean decrease in sodium was 42%, potassium 33%

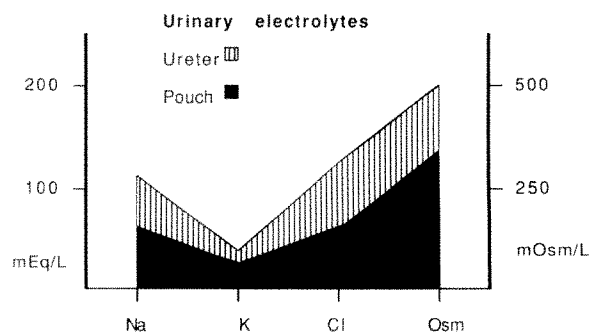


Fig. 2 Comparison of levels of urinary sodium, potassium, chloride and osmolality between ureteric and pouch urine. Values of electrolytes and osmolality decreased by a mean of 32 to 48% between ureteric and pouch urine.

Table 2 Serum Chemistry of 11 Patients with Mean Follow-up of 10 Months after Mainz Pouch Construction

Normal range	Before operation	After operation
Na (135–140) mEq/L	139 (134–143)	141 (138–145)
Cl (90–106) mEq/L	103.4 (97–107)	107 (102–112)*
K (3.5–5) mEq/L	4.3 (3.6–4.8)	4.5 (4–4.9)
CO ₂ (24–32) mg/dl	25 (20–32)	23 (19–25)†
Cr (0.6–1.5) mg/dl	1.2 (0.9–2.0)	1.2 (0.2–2.3)
BUN (10–24) mg/dl	14 (7–23)	21 (13–31)
B ₁₂ (200–900) pg/ml	—	248 (116–369)‡

* Six patients were hyperchloraemic (> 106 mEq/L).

† Three patients were hypocarbic (< 24 mg/dl).

‡ All patients had low B₁₂ levels (2 were < 200 pg/ml).

and chloride 48%). This absorptive trend obligates the pouch patient to excrete greater volumes of free water per daily solute load. The mean decrease in urine osmolality in the pouch was 32%. Serum survey after a mean of 10 months revealed mild hyperchloraemia in 6 patients with associated hypocarbia in 3. All patients had low levels of B₁₂. None was found to have macrocytic anaemia (Table 2). No significant alterations in Ca or Mg have been found.

Bacteriological studies

There have been no febrile urinary tract infections. Routine post-operative urine analysis revealed persistent mucous threads and leukocytes. Urine cultures from patients on intermittent self-catheterisation revealed mixed colonies with counts of 100,000 CFU/ml. All 6 voiding patients have either sterile urine or counts below 1000 CFU/ml.

Urodynamic studies

Functional changes in urethral pressure profile length were difficult to demonstrate with normal pull-through urodynamic techniques. Patients maintained an average of 83% of their pre-operative peak urethral pressure.

At 1 to 3 months the mean capacity of the pouch was 395 ml (range 250–700) with an increase to 830 ml (range 500–1200) at 6 months (Fig. 3) (Table 3). Peristaltic pressure waves with patient-specific amplitudes and frequencies were noted in all pouches despite detubularisation and reconfiguration of the bowel. They were most pronounced in the first 4 to 6 months post-operatively and decreased as pouch capacity rose. In some, however, the pressure waves remain prominent even at 12 to 18 months of follow-up. Continence is maintained during these pressure waves by phasic increases in external sphincteric tone that exceed the amplitude

of the pouch pressure (Fig. 4) (Broderick *et al.*, 1989). Pressure waves range from 20 to 80 cm H₂O. Resting pouch pressure at full capacity ranges from 10 to 16 cm H₂O.

Nocturnal incontinence in patients with ileocaecal pouches appears to be a result of urethral sphincteric relaxation associated with sleep. We performed 8-h nocturnal urodynamic studies in 4 patients and found that the increases in urethral pressure associated with peristaltic pressure waves in the pouch noted in the awake patient are not present during deep sleep (Fig. 5). During sleep there are variations in urethral sphincter tone, and pouch peristalsis persists. At high volumes, these contractions result in urinary leakage that is prevented if the patient keeps the intravesical volume low by voiding every 4 to 6 h.

Complications

Three patients developed strictures at the entero-urethral anastomosis. Two required visual urethrotomy at 11 and 13 months that was limited to shallow incisions made with a hook blade at the 3 and 9 o'clock positions.

One patient still has a suprapubic tube. In this patient, transverse colon and proximal ileum were used for pouch construction because a right hemicolectomy was required for an incidentally discovered caecal cancer. Because of this modification in technique, non-detubularised proximal ileum was anastomosed to the urethra in an end-to-side fashion. This patient developed a 3-cm enterourethral anastomotic stricture. Two attempts at endoscopic correction failed. Although enterourethral continuity was re-established endoscopically, the stricture recurred after the urethral catheter was removed at 3 weeks and 6 weeks. The patient has opted for suprapubic drainage, refusing conversion to a continent catheterisable stoma. A second

Table 3 Functional Characteristics of Mainz Pouch

	Months after operation	
	1–3	6–12
Capacity (ml)	395 (250–700)	830 (500–1200)
Reservoir pressure at capacity (cm H ₂ O)	13 (10–20)	16 (10–20)
Filling volume at first contraction (cm H ₂ O)	180 (100–250)	285 (150–500)
Maximum reservoir pressure during contraction (cm H ₂ O)	48 (20–60)	40 (20–80)

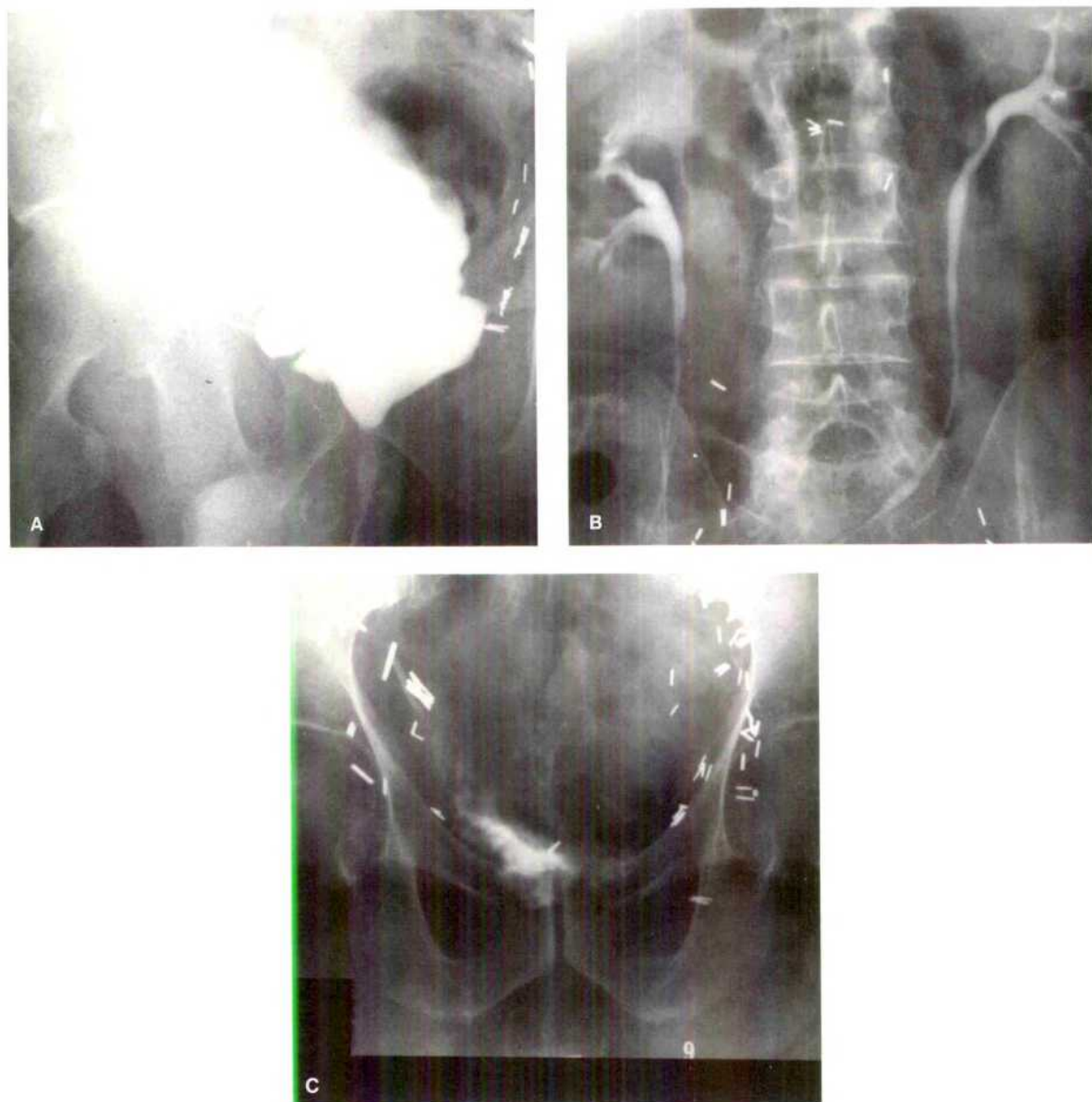


Fig. 3 Intravenous urogram and voiding study. (A) Typical voiding pouchogram of patient with ileocecal bladder substitute 6 weeks post-operatively. (B) Intravenous urogram demonstrating normal excretion bilaterally with no evidence of ureteric dilatation. (C) Post-void film demonstrating minimal residual urine.

patient needed a temporary suprapubic tube because of disruption of a perineal urethrotomy after a few weeks of normal voiding. The disruption occurred during his second course of adjuvant cancer chemotherapy. The urethrostomy had been created and closed primarily for the initial transurethral resection of bladder cancer because he had a semi-rigid penile prosthesis. The suprapubic tube

was removed 3 weeks after completion of his chemotherapy.

One patient developed gastrointestinal bleeding manifested by melaena on the fifth day post-operatively. This was clearly related to the warfarin sodium prophylaxis as his prothrombin time was elevated to 2.5 times his normal value at the time of bleeding. No therapy other than transfusion of 2

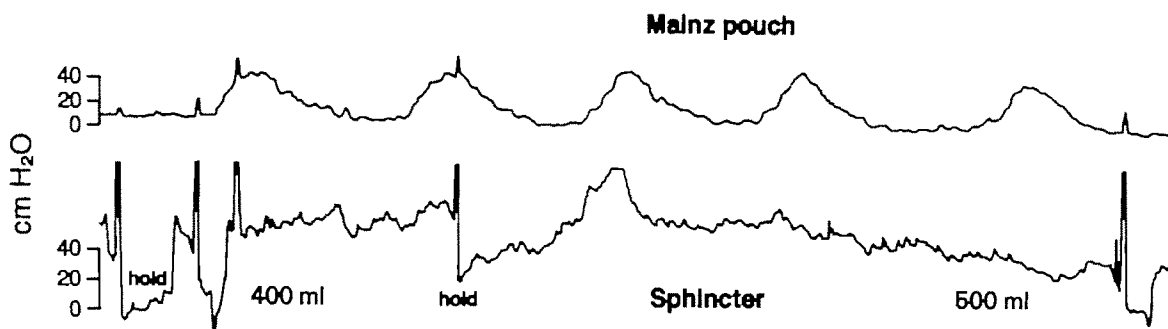


Fig. 4 Urodynamic profile of a patient 1 year after Mainz pouch construction. Note that the propagation of reservoir waves cannot be suppressed by voluntary control of the sphincter. Sphincteric control manoeuvres were performed on command. For urodynamic studies, the inflow rate was 50 ml/min, pouchometry was performed with a 7 F 3-membrane catheter (Mentor), recordings were made on DISA-Dantec URO-system.

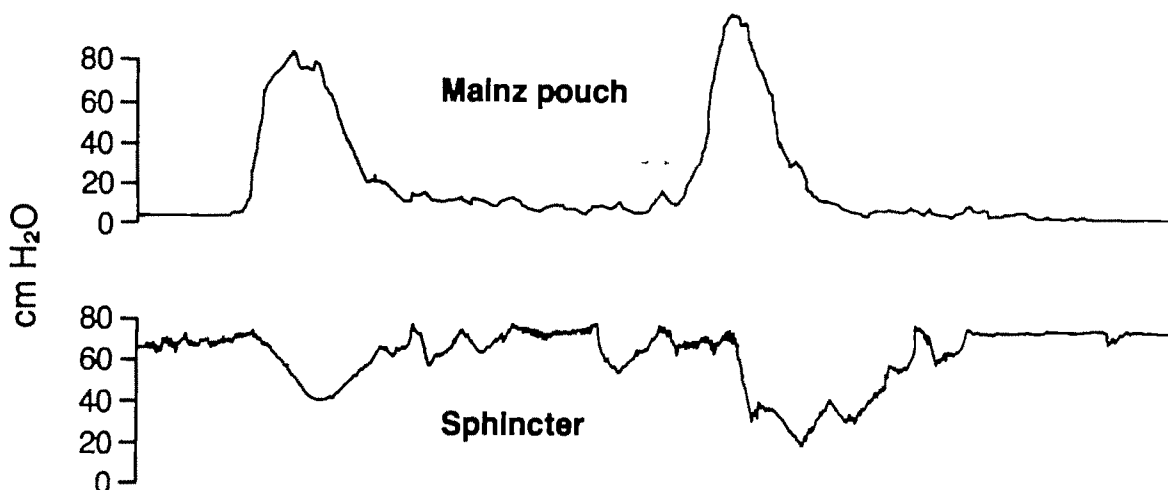


Fig. 5 Nocturnal studies performed on the same patient (5-min intervals). Pouch contractions continue during sleep. During physiological filling, the amplitude of pressure waves increases with increasing pouch volumes. Peak contraction pressures at night were equal to those noted during standard "pouchometry" for all intervals of follow-up. The phasic increases in urethral pressure noted during awake studies failed to occur during sleep. The study was done with a Galectec MMI silicone catheter (16 CT/ST) with 3 direct pressure sensors.

units of packed red cells and discontinuation of coumarin was required.

Discussion

The ultimate choice of a bowel segment for continent diversion will be determined by the long-term results of the several procedures now in use. Hinman (1990) has outlined several principles that should guide the urological selection of bowel for bladder substitution. First, geometric reconfiguration must be considered: volume rises by the square of the radius. The second consideration is accommodation: at any physiological pressure the reser-

voir with the larger radius will hold a greater volume. The third is compliance. However, little difference in the viscoelastic properties of bowel segments persists after 6 months. Finally, there is contractility: disruption of normal tubular structure will blunt intraluminal pressure spikes.

The technique of detubularisation by Nils Kock is a significant contribution that has led to the recent popularity of bowel neobladders. The Kock pouch uses small bowel (which has lower intrinsic pressures than large bowel) with detubularisation and reconfiguration to reduce intrinsic pressures further and intussusception to prevent reflux and provide continence (Kock *et al.*, 1982). The princi-

pal advantages of the ileocaecal segment over use of small bowel are: (a) the location of the caecum, which allows easy enterourethral anastomoses; (b) the ileocolonic segment, which lends itself to the creation of a continent stoma either by intussusception or plication; (c) the relative surgical simplicity in both pouch construction and antireflux ureteric implantation; (d) use of a shorter bowel segment, which is theoretically less likely to cause metabolic problems from absorption of electrolytes and urea nitrogens.

Pressure studies of detubularised ileal and large intestinal segments suggest that the amplitude of contractions is higher in large bowel. The use of intact sigmoid colon with its high-amplitude pressure waves has necessitated placement of artificial urinary sphincters in about 70% of patients (Reddy *et al.*, 1987). However, intact small bowel also has high-amplitude pressure waves. Recently, Camey has advocated detubularising ileum in his operation to decrease pressure waves and resulting short voiding intervals and incontinence (personal communication). Our own studies reveal persistent pressure waves in the ileocaecal segment at 2 years. With time, however, the amplitudes of these pressure waves steadily decrease and volumes increase. Daytime continence is always obtained with this technique, and nocturnal continence is achieved with an acceptable 4-h voiding schedule. It appears that nocturnal leakage in these patients results from relaxation of the external sphincter, as first suggested by Hradec in 1965. Our studies confirm these findings (Broderick *et al.*, 1989).

Technically, the construction of the Mainz pouch is easily learned. We have had no complications of urinary leakage when using a 2-layer closure with either 3-0 Maxon or Dexon. There have been no febrile episodes consistent with "pouchitis." Urinary reflux has not been a problem; we found that making a ureteric tunnel longer than 2–2.5 cm can result in upper tract dilatation.

The metabolic sequelae of bladder substitution depend on the segment of bowel chosen, its length, the duration of exposure to urine and the patient's pre-operative renal function. Lilien and Camey (1984) reported a low incidence of metabolic acidosis and both Kock *et al.* (1978) and Skinner *et al.* (1984) reported a low incidence of metabolic acidosis with the Kock pouch. Our studies demonstrate increased absorption of sodium, chloride and potassium from the ileocaecal pouch urine, but serum electrolyte values reflect only mild hypocarbia in a minority of patients. Chemotherapy has adversely affected renal function in our patients,

which may indeed have been aggravated by reabsorption of urea nitrogens and electrolytes across pouch mucosal surface. No patient has required therapy for metabolic acidosis.

The incidence of decreased serum B₁₂ levels in our patients was noteworthy, but no megaloblastic anaemia developed over a mean of 6 months. Supplemental B₁₂ injections have been initiated quarterly.

The ideal bladder substitute should allow the patient to maintain his body image and void normally. However, this goal should not be reached by compromising standard oncological surgery. Preservation of apical prostatic tissue or capsule has been advocated for specific reservoirs (McDougal, 1986; Zinman and Libertino, 1986). Our data and those of others reveal a significant incidence of concurrent carcinoma of the prostate in cystoprostatectomies performed for transitional cell cancer (Mahadevia *et al.*, 1987; Winfield *et al.*, 1987). When adequately excised, however, concomitant carcinoma of the prostate may not be an additional risk factor in these patients. In a 12-year follow-up of patients with bladder cancer and incidental prostatic cancer, Androulakakis *et al.* (1986) found that prognosis was dependent only on the stage and grade of the bladder cancer.

The incidence of concurrent urethral and bladder transitional cell cancer is approximately 7% (Schellhammer and Whitmore, 1976). We do not routinely perform urethrectomy unless pre-operative evaluation reveals prostatic urethral involvement or frozen sections show cancer at the urethral margins. In a patient with a neobladder the urethra will continue to be exposed to potential carcinogens. It is prudent, therefore, to continue endoscopic and cytological examination of the urethra in these patients. Biopsies of Kock pouches after several years of follow-up reveal changes in the bowel mucosa with loss of microvilli and crypts but no evidence of metaplasia or malignancy. However, adenocarcinoma of both large and small bowel has been reported after their use for urinary diversion (Hammer, 1929; Shapiro *et al.*, 1979; Merctyk *et al.*, 1987). The urologist performing bladder substitutions for cancer is, therefore, obligated to continue radiographic and endoscopic surveillance of these patients over the long term.

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Clinical Experience with Subcutaneous Urinary Diversion: New Approach Using a Double Pigtail Stent

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Summary—Short-term results in 8 patients with ureteric obstruction and hydronephrosis who underwent subcutaneous urinary diversion show this procedure to be a simple and useful method of urinary diversion for uraemic cancer patients. This method has the additional advantage of avoiding the complications and social implications of other methods of palliative treatment.

Until recently, urinary diversion via a percutaneous nephrostomy was a popular method of palliative treatment of uraemic cancer patients (Fallon and Culp, 1980; Chiou *et al.*, 1990). However, several complicating factors often make the procedure unacceptable to both the patients and their families: additional urinary infection due to the nephrostomy, the nursing care associated with the nephrostomy tube and its effect on the patients' social and psychological wellbeing. Even though it is understood that without some form of urinary diversion their chances of survival decrease significantly following the development of uraemia (Chiou *et al.*, 1990), many patients refuse to have a nephrostomy.

Many aetiologies have been proposed for ureteric obstruction and hydronephrosis in cancer patients. The most common primary tumours that cause ureteric obstruction and hydronephrosis are those of the cervix and the prostate. Other causes are cancer of the bladder, urethra and breast (Grabstald and Kaufman, 1969), gastrointestinal malignancies, lymphoma, and the complications of irradiation. As treatment for these conditions in advanced cancer patients, open nephrostomy carries considerable risks (Holden *et al.*, 1979) and simple percutaneous nephrostomy is usually preferred. A ureteric stent can be an alternative to a nephrostomy in these patients, but it is not always possible to place a ureteric stent in the urogenital tract (Hepperlen *et al.*, 1979; Zadra *et al.*, 1987).

Subcutaneous urinary diversion is another alternative. The technique is easily learned, well tolerated by the patient, and is indicated when other urological procedures for alleviating hydronephrosis and uraemia in cancer patients are unsuitable.

Patients and Methods

Between June 1987 and February 1989, 8 patients, ranging in age from 68 to 83 years, underwent subcutaneous placement of a double pigtail stent (Braun Melsungen AG, Germany) as a urinary diversion. All had advanced prostate carcinoma associated with tumour infiltration and ureteric obstruction, hydronephrosis and uraemia.

This palliative treatment with subcutaneous urinary diversion addresses the problems associated with the continuous nursing care of a nephrostomy tube, which become particularly evident when no-one is available to perform this function—the tube may eventually be dislodged when the patient moves.

We select patients for subcutaneous urinary diversion according to their general condition, the degree of hydronephrosis and the serum creatinine level.

Pre-operatively, we undertake renal function studies, urine culture and intravenous urology (IVU) on all patients. We perform renal ultrasonography to study the renal outlines and collecting system in longitudinal and transverse section; this procedure also demonstrates the degree of hydro-

nephrosis. Finally, if the serum creatinine level is no higher than 2 mg/100 ml (176.9 $\mu\text{mol/l}$), we perform an IVU to locate the site of the obstruction (Sökland *et al.*, 1987).

After cystoscopy, we try to stent the ureter when ureteric stenosis is minimal following local tumour extension or a previous transurethral resection; otherwise a simple percutaneous nephrostomy is the treatment of choice (Culkin *et al.*, 1987; Chiou *et al.*, 1990). Theoretically, it is possible to stent most ureters, but in cases of ureteric stenosis caused by pelvic malignancy it is often unsuccessful (Hepperlen *et al.*, 1979; Zadra *et al.*, 1987). Endoureterotomy and placement of a double pigtail stent are feasible when there is a narrow passage in the ureter.

General anaesthesia was used initially, although it has since been found that patients can tolerate spinal or even local anaesthesia. Percutaneous nephrostomy is performed on the radiosonograph-

ically superior kidney (Baron *et al.*, 1981). After percutaneous puncture of the collecting system and aspiration of the accumulated urine, the puncture site is dilated to 12F using a balloon dilator or metal telescope dilators (Alken, 1981; Stables, 1982). A special drainage set (Braun Melsungen AG, Germany) was designed for this operation. The polyethylene double pigtail stent varies from 50 to 60 cm and 11F in diameter.

After placing the upper end of the stent in the renal pelvis, a small incision (approximately 2 cm in length) is made in the skin at the puncture site. A piece of silicon wound drainage tube (approximately 15 mm and 8 mm in diameter) is passed over the stent. The stent is placed in subcutaneous tissue, which prevents kinking at the puncture site, and is secured with a 3-0 prolene suture (Fig. 1).

The lower end of the stent is connected to a Redon stylet and advanced subcutaneously. Because of the short stylet length, 2 small skin

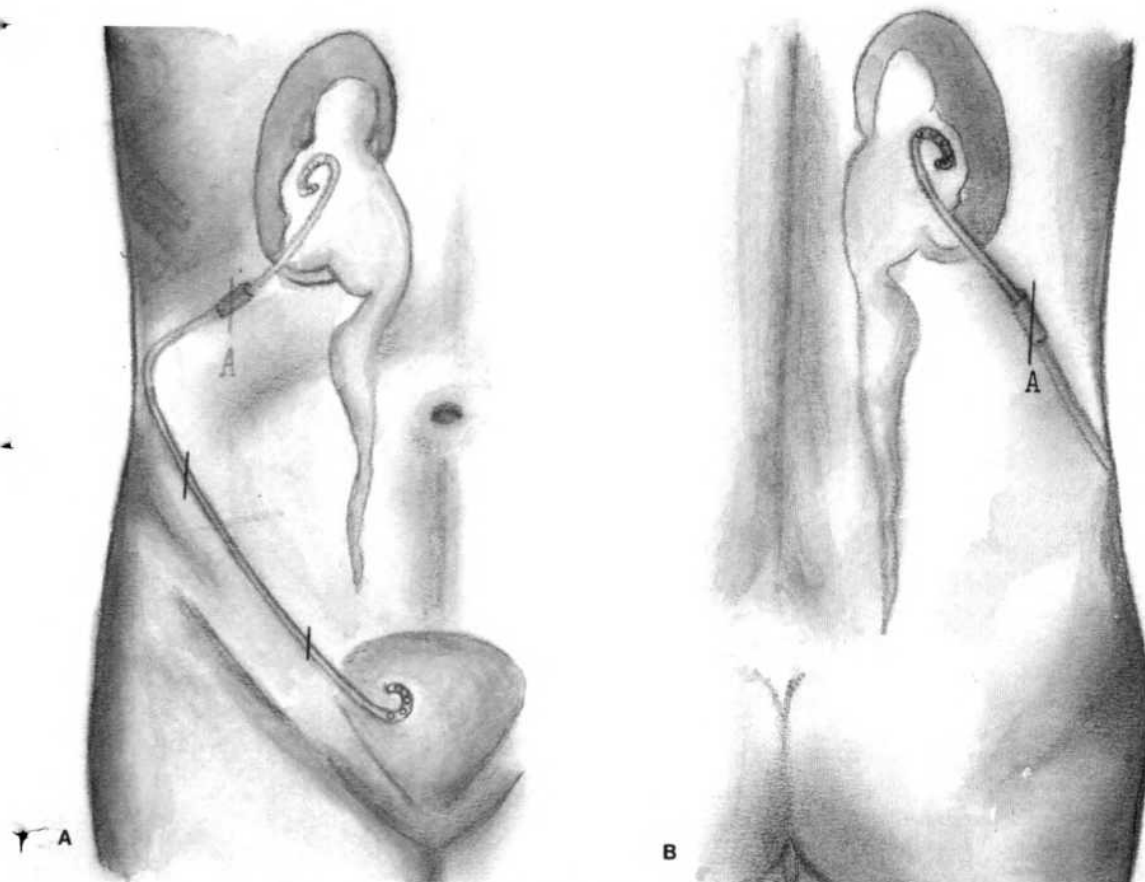


Fig. 1 (A) Position of double pigtail stent in urinary diversion (anterior view). (B) Nephrostomy catheter is implanted subcutaneously (posterior view).

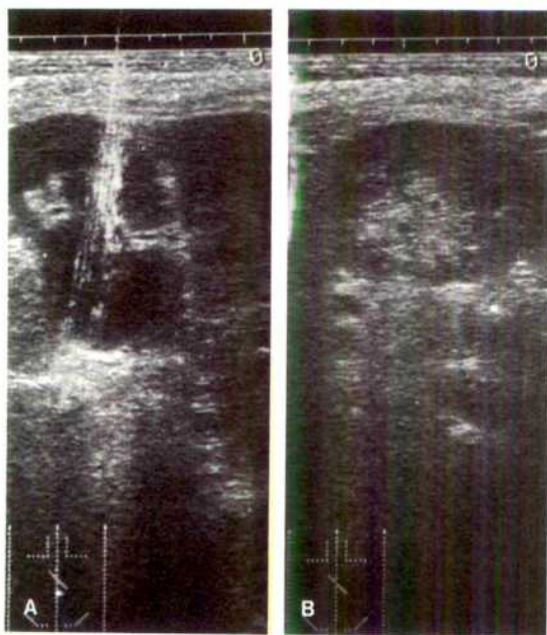


Fig. 2 (A) Pre-operative renal ultrasound in patient with advanced prostate cancer (right kidney). (B) Post-operative renal ultrasound in same patient 4 months later.

incisions may facilitate this advancement; the second incision must be made near the bladder. After inserting the double pigtail stent subcutaneously in the abdominal wall, the lower part of the stent is passed into a pre-split trocar and advanced obliquely into the bladder. This can be facilitated by filling the bladder prior to surgery. Finally, the skin is sutured using 3-0 Dexon.

The upper urinary tract is evaluated post-operatively by ultrasonography (Fig. 2), urine culture and serum creatinine levels. All patients tolerated the procedure well and there was no bleeding. Some experienced mild to moderate pain after the nephrostomy, but this was relieved with minor analgesics.

To change the stent, it is sufficient to reincise (at point A in Fig. 1B), remove the suture and cut the stent, tying it with a 70 cm length of monofilament thread. The stent can be removed through a cystoscopy. We attach the thread to the upper end of a new ureteric stent and pull it from point A. Finally, with the assistance of a guide wire, the upper end of the new stent is placed in the collecting system. This procedure can be performed under local anaesthesia.

In the absence of complications, follow-up

appointments and stent changes are made at 3-monthly intervals.

Results

All 8 patients in the series had advanced prostate carcinoma with hydronephrosis and uraemia. Four have since died from their primary malignancy and disseminated metastases, but none has died from uraemia. In 7 cases post-operative ultrasonography improved as a result of this procedure. In 1 patient the stent became obstructed 3 times in 1 month; this patient refused subcutaneous urinary diversion and we performed a simple percutaneous nephrostomy.

There were no major complications after subcutaneous urinary diversion or after changing the stents. The average length of follow-up has been 18 months (range 6–30).

Discussion

Pelvic malignancy associated with ureteric obstruction has a poor prognosis (Fallon and Culp, 1980; Dowling *et al.*, 1987). Survival after nephrostomy, in a patient who has failed hormonal therapy, radiotherapy and chemotherapy, usually ranges from 1 to 24 months (Holden *et al.*, 1979). Many factors can be responsible for the patients' deaths.

In uraemic conditions a retrograde placement in the ureter of a double pigtail stent (or a simple percutaneous nephrostomy) can increase survival and improve the quality of life (Zadra *et al.*, 1987). When survival is expected to be short because of other factors, the value of these procedures may be questioned. Factors such as the response of the tumour to conventional treatment and the influence of the family on further therapy must also be considered.

Subcutaneous urinary diversion can be performed in patients who live alone and who would experience difficulty in caring for a nephrostomy tube, or in situations where the patient does not want an external appliance because of social or psychological reasons. This procedure minimizes the risk of urinary infection and sepsis (Hannapel *et al.*, 1986). It is a simple technique which can easily and safely be performed in patients with advanced cancer.

Acknowledgement

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Multi-centre Phase II Study of Low Dose Intravesical Epirubicin in the Treatment of Superficial Bladder Cancer

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Summary—Forty patients with multiple recurrent superficial bladder tumours received an 8-week course of weekly instillations of 4' epirubicin 30 mg in 50 ml saline. The overall response rate was 58% and side effects were minimal.

Among the effective intravesical agents used for the treatment of recurrent superficial bladder cancer the anthracyclines (Adriamycin) have been shown to be effective both therapeutically (Matsumura *et al.*, 1983) and prophylactically (Nijima *et al.*, 1983). Despite their large molecular size and consequent poor absorption across the bladder wall, these compounds are nonetheless associated with local and systemic side effects (Crawford *et al.*, 1986). Epirubicin (the 4' epiadriamycin derivative) has been reported by Bonfante *et al.* (1982) to produce the same therapeutic response as its parent compound, but with a lower incidence of side effects. In our first report on patients receiving 50 mg in 50 ml saline, this was not the case and 30% of patients failed to complete the course because of local and systemic side effects (Cumming *et al.*, 1990). We have now assessed the response of 40 patients to a lower dose of 4' epirubicin (30 mg in 50 ml saline) and also noted the incidence of side effects.

Patients and Methods

The study was confined to patients with difficult and recurrent superficial transitional cell carcinoma of the bladder. All had received many transurethral

resections for recurrent superficial bladder tumours and 2 patients had previously received 50 mg 4' epirubicin in 50 ml saline weekly for 2 months. This treatment had ceased 1 month and 5 months prior to their entering the study.

Between March 1986 and December 1988, 40 patients (27 males and 13 females) with a mean age of 68.8 years (range 39–92) were studied. All had been cystoscoped and their pathological grade and stage determined prior to entry (Table 1). Follow-up was for a minimum of 12 months.

The tumour load was categorised as involving more than 50% of the bladder (9 patients), multiple but discrete superficial lesions (13), large areas of superficial tumour which could be biopsied but not

Table 1 Initial Staging and Grading of Tumour

	No. of patients
TaG1	10
TaG2	8
TaG3	2
T1G1	6
T1G2	6
T1G3	1
T2G1	1
T2G2	1
Tis	3

It is noteworthy that the 3 patients with Tis tumours and the 2 with biopsy-proven invasive tumours (T2G1, T2G2) failed to respond.

completely resected (15) or the whole of the bladder appearing red and inflamed (3). The response criteria are shown in Table 2.

Base-line samples were taken for full blood count, platelet estimation, urea and electrolytes and liver function tests. All patients had a chest X-ray and a 12-lead electrocardiogram prior to entry.

The patients received an intravesical dose of 30 mg 4' epirubicin in 50 ml normal saline, and this was retained for 60 min. The instillations were continued weekly for a total of 8 weeks and the patients were reviewed for adverse symptoms at each instillation, with urine being sent for bacteriological examination and blood taken for full blood count. At weeks 3 and 7, blood was checked for urea and electrolytes and also liver function tests. In the case of proven urinary tract infection, the appropriate antimicrobial therapy was instituted and further instillations were deferred until the urine was bacteriologically sterile. Cystoscopy was repeated within 7 days of completion of the course and again approximately 4 weeks after completion. Follow-up continued on a 3-monthly basis thereafter.

Results

Of the 40 patients entered, 2 were not considered evaluable for treatment response. The first (aged 92) received only 4 instillations at fortnightly intervals and was then followed up with urine cytology alone. The second patient complained of burning 1 week after his first instillation and received no further treatment. Of the remaining 38 patients, 9 were judged to have had a complete response at cystoscopy carried out within 4 weeks of completion of treatment (Table 3). This showed no evidence of visible tumour, and biopsies of sites where tumour had been present were negative. This complete response was sustained throughout the 12-month evaluation period, although 3 of these patients developed small single superficial recurrences which were treated by local diathermy alone.

Table 2 Response Criteria

Complete response:	complete disappearance of tumour confirmed by biopsy
Good response:	response enabling transurethral resection of residual tumour, with negative biopsies of previously identified tumour sites
No response:	no change in residual tumour area with additional tumour growth

Table 3 Response by Pathological Stage and Grade

	Complete response	Good response	Progression
TaG1	3	5	2
TaG2	2	2	4
TaG3	0	1	1
T1G1	3	1	2
T1G2	1	3	2
T1G3	0	0	1
T2G1	0	0	1
T2G2	0	0	1
Tis	0	0	3
Totals	9	12	17

Twelve patients had a good response in that the tumour was readily controlled after the course of treatment by further endoscopic resection; 7 of these patients remained controlled over the 12-month evaluation period but 5 required additional treatment; in all cases this consisted of further diathermy, although they had developed further recurrences. The remaining 17 patients showed no evidence of response at the first cystoscopy and all subsequently showed evidence of progressive disease; 2 underwent cystectomy and 4 died during the evaluation period from carcinoma of the bladder.

Complications

Complications of intravesical treatment were minimal. One patient had chemical cystitis and treatment was delayed for 1 week; 8 patients had mild degrees of haematuria but all settled on non-specific measures and in only 1 case was treatment deferred for 1 week. In a total of 248 instillations, there were 27 episodes of positive bacterial growth, giving an overall infection rate of 10.8%. These and other complications are shown in Table 4.

Discussion

Adriamycin is effective both therapeutically and prophylactically in the treatment of superficial bladder carcinoma. It has been associated with troublesome side effects such as chemical cystitis, cardiotoxicity, alopecia, thrombocytopenia and marrow suppression. In our previous study (Cumming *et al.*, 1990), using a higher dose of 4' epirubicin (50 mg in 50 ml saline), 32% of patients failed to complete their course of treatment because of side effects, and 35% of them were judged to have had at least 1 episode of chemical cystitis necessitating delay in instillation.

Table 4 Complications of Treatment

<i>Bacterial growth (27 of 248 occasions—10.8%)</i>			
<i>Patient</i>	<i>Occasions</i>	<i>Delay in treatment</i>	<i>Bacteria</i>
1	1	1 week	UTI* mixed bacterial growth
2	2	No delay	<i>Strep. faecalis</i> (10)
3	3	No delay	<i>Streptococcus</i> (10)
			<i>Strep. faecalis</i> × 1
			UTI mixed bacterial growth
4	1	No delay	<i>Candida</i> 10–10
5	2	No delay	<i>Strep. faecalis</i> 10
6	1	No delay	<i>Klebsiella</i> + <i>Proteus</i> 10
7	1	1 week	UTI (presented with pseudo-Ar†)
8	1	3 week	Coliform + pseudo Ar 10
	2	No delay	<i>Strep. faecalis</i>
9	2	No delay	<i>Proteus</i> 10 × 2
10	3	No delay	<i>Strep. faecalis</i> × 3
	1	No delay	Scanty bacterial growth
11	4	1 week	Coliform 10 × 4
12	2	2 weeks	<i>Staph albus</i> 10
13	1	1 week	UTI mixed bacterial growth

*UTI: urinary tract infection.

†Ar:

The tumour response, however, was similar to that of the present study and the adverse effects appeared related purely to the concentration of 4' epirubicin. Using the lower dose of 30 mg in 50 ml, there were minimal side effects and the response rate (59% versus 58%) was similar.

In this particular group of patients, whose tumours were difficult to control and who had multiple recurrences, the instillation of 4' epirubicin produced a complete response in 9/38 patients (24%) and effective control in a further 13 (35%). Two patients had T2 tumours and probably should have had earlier definitive and radical treatment. The 3 patients with carcinoma *in situ* did not respond and it is possible that other intravesical agents, such as BCG, would have been more successful.

In a group of highly selected patients with recurrent superficial bladder tumours, of all stages and grades, treatment with 4' epirubicin enabled a significant number to be controlled by local means alone. The responses were sustained for at least 12 months and it is possible that the progressive nature of their disease has been contained and effectively

controlled. There were no objective criteria such as frequency of recurrence, stage, grade or volume of tumour which enabled a pre-treatment prognosis to be made, and we recommended therefore, in these difficult tumours, a trial of 4' epirubicin 30 mg in 50 ml saline intravesically, weekly for 8 weeks. Failure to respond at the first check cystoscopy implies that more aggressive treatment is necessary, for these patients are at significant risk from their disease, as can be seen from the deaths of 4 non-responders in the 12 months following treatment.

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Cisplatin Combination Chemotherapy for Elderly Patients with Urothelial Tumours

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Summary—The proportion of cancer patients who receive potentially curative therapy declines with increasing chronological age. Between January 1979 and January 1988, 36 patients aged from 76 to 84 years (median 78) consented to cisplatin combination chemotherapy. Eighteen patients received 1 to 7 cycles of adjuvant chemotherapy (median 5). This resulted in a drop in creatinine clearance rate from 70 ± 28.5 ml/min to 49 ± 20 ml/min. Eight patients (44%) are alive without evidence of disease, with a whole group median survival of 23 months. The dose intensity of cisplatin was found to predict recurrence. Eighteen other patients were treated for metastatic disease; 39% had an objective response after receiving 2 to 9 cycles (median 7). Only 2 patients (11%) are alive and free of disease. In this group no significant kidney damage occurred and the dose intensity of cisplatin did not predict response. Treatment resulted in a significant sepsis rate (39%) and 6 patients (17%) withdrew from treatment because of toxicity.

It was concluded that cisplatin combination chemotherapy can be administered without treatment-related death and its efficacy is similar to that in younger patients. Age should not exclude patients from the potential benefit of such therapy. An important cause of reduced benefit from chemotherapy among elderly patients may be the reduced dosage of cisplatin.

Improved response rates have been reported from a variety of regimens used for patients with advanced bladder cancer (Logothetis *et al.*, 1988; Sternberg *et al.*, 1988; Lo *et al.*, 1989). However, there is no firm evidence that patients derive significant benefit from these therapies, although subsets of patients have achieved long-term disease-free survival. The role of adjuvant chemotherapy in bladder cancer has not been clearly established, although reports have indicated the usefulness of cisplatin combination chemotherapy for patients who are at a high risk of relapse following definitive surgical resection (Logothetis *et al.*, 1988). However, these reports do not show whether the efficacy and toxicity of the various forms of treatment differ in elderly patients. This may explain the hesitation to recommend aggressive cisplatin combination chemotherapy in older patients, in whom significant

toxicity has been observed following chemotherapy (Walsh *et al.*, 1989). We report our experience with aggressive cisplatin combination chemotherapy in elderly patients with urothelial tumours.

Patients and Methods

Between January 1979 and January 1988, 43 patients more than 76 years old who had urothelial tumours were referred for an evaluation of their eligibility for systemic chemotherapy. Determining factors included clinical status and evidence from surgical specimens, all of which were assessed by pathologists at this hospital.

Two groups of patients were identified. Group 1 comprised patients at high risk of relapse following cystectomy or nephroureterectomy, for whom adjuvant chemotherapy was recommended. Indications were determined by pathological examination of the resected specimens and included histological

evidence of vascular invasion in the primary tumour, nodal metastases, contiguous invasion of adjacent organs (vagina, prostate), and extraureteric or extravesical invasion. Group 2 comprised patients with measurable metastatic disease in whom treatment of the primary tumour (surgical resection, definitive radiation therapy) had failed or who had presented with unresectable disease.

Clinical criteria for eligibility included a creatinine clearance rate >40 ml/min, a cardiac ejection fraction of 40% or more without clinical evidence of congestive heart failure, performance status <4 (an Eastern Cooperative Oncology Group standard) and no active infection.

Histological criteria for eligibility included the presence of transitional cell carcinoma with or without mixed tumour. Mixed tumour was defined as one containing transitional cell carcinoma and one or more other histological subtypes (squamous cell carcinoma, adenocarcinoma, sarcoma). Patients with pure adenocarcinoma were excluded.

A total of 36 patients agreed to receive cisplatin-based chemotherapy, which included CISCA (cyclophosphamide $500\text{--}650$ mg/m² body surface area [BSA] day 1, doxorubicin 50 mg/m² BSA day 2, and cisplatin 100 mg/m² BSA day 2: 16 patients), M-VAC (methotrexate 30 mg/m² BSA days 1, 15 and 22, vinblastine 3 mg/m² BSA days 1, 15 and 22, doxorubicin 30 mg/m² BSA day 2, and cisplatin 70 mg/m² BSA day 2: 12 patients), or CMV (cisplatin 100 mg/m² BSA day 2, methotrexate 30 mg/m² BSA days 2 and 8, and vinblastine 4 mg/m² BSA days 2 and 8: 8 patients). All doses of cisplatin were given with simultaneous forced mannitol diuresis. Prerequisites to receiving the initial course of chemotherapy included the absence of stomatitis or infection, a platelet count $>100,000$ and a granulocyte count >2000 . Patients receiving either M-VAC or CMV were given booster doses of methotrexate and vinblastine if their granulocyte count exceeded 500 and platelet count $>50,000$ without evidence of stomatitis or infection. Therapy was reduced by 20% in the case of grade 3–4 haematological toxicity (WHO), cisplatin was reduced to 50 mg/m² if creatinine clearance fell below 40 ml/min, and it was omitted when creatinine clearance fell below 30 ml/min. All 3 regimens have been described previously (Logothetis *et al.*, 1988; Sternberg *et al.*, 1988; Lo *et al.*, 1989).

Three categories of response were used: (1) progressive disease: any new sites of neoplastic disease that developed during therapy, response that was less than partial or symptomatic deterioration; (2) partial response (PR): $>50\%$ decrease

in all measurable disease, measured by the sum of 2 perpendicular diameters; (3) complete response (CR): complete disappearance of all clinical and radiographic evidence of disease, including cystoscopic abnormalities. Pathological confirmation of CR was not required.

Survival was calculated from the initiation of systemic chemotherapy. All patients monitored at other institutions after completing treatment were contacted by telephone and data were obtained from their personal physicians. No patient was lost to follow-up. Student's *t* test was used in the statistical analysis.

The drug common to the 3 regimens was cisplatin. Since cisplatin is more effective than the other drugs in the above regimens (Ackland and Vogelzang, 1988), we attempted, by applying Hryniuk's dose-intensity calculation, to correlate the dose intensity of the actual delivered cisplatin with the outcome of each of the 3 regimens in this population (Hryniuk *et al.*, 1987). The data on the delivered cisplatin dose intensity represent the percentage from the anticipated dose intensity with its standard deviation.

The study group included 7 women (19%) and 29 men (81%); their median age was 78 years (range 76–84). The tumour originated in the bladder in 30 patients (83%) and in the upper tract in 6 (17%); 27 patients (75%) had transitional cell carcinoma and 9 (25%) had transitional cell carcinoma plus a mixed element. All patients met our eligibility criteria; the pre-chemotherapy creatinine clearance rate was 69 ± 24 ml/min and the cardiac ejection fraction was $67\% \pm 9.9\%$.

Results

Group 1 (adjuvant therapy)

Eighteen patients were included in this group. Four patients (22%) had stage T2 carcinoma, all with vascular invasion; 5 (28%) had stage T3 disease, 3 (17%) had T4 disease and the remaining 6 (33%) had T4 N2 M0 tumours. Primary treatment included radical cystectomy (16 patients), and partial cystectomy and nephroureterectomy in the other 2.

The patients' performance status was good, with a median of 1.0. Their cardiac ejection fraction was $65.3\% \pm 11.9\%$ and their 24-h creatinine clearance rate was 70 ± 28.5 ml/min. We planned to give 5 cycles of chemotherapy to each patient. The median number of treatments was 5 but ranged from 1 to 7. The dose intensity of cisplatin was $52\% \pm 25.3\%$.

- Five patients (28%) withdrew from treatment owing to toxicity (myocardial infarction, recurrent urinary sepsis), patient refusal (diarrhoea due to pseudo-membrano-colitis, otitis media) and progression of disease (1 patient). Six patients (33%) had infectious complications which, in addition to those that resulted in termination of therapy, included 3 episodes of uneventful fever of unknown origin. Treatment resulted in significant renal toxicity and a deterioration in creatinine clearance rate to 49 ± 20 ml/min ($P=0.01$).
- Eight patients (44%) are alive without evidence of disease and 10 have relapsed. The median survival was 23.0 months (range 4–42+); 7 patients (39%) have succumbed to their disease (Fig.).

The dose intensity of delivered cisplatin was found to predict recurrence. Cisplatin dose intensity was $64.4\% \pm 21.8\%$ for patients who are now free of disease and $42.1\% \pm 24.3\%$ for those who have relapsed ($P=0.03$). Although 55% of patients with transitional cell carcinoma are free of disease as compared with 29% of those with transitional cell and mixed carcinomas, tumour type did not correlate significantly with relapse ($P>0.05$).

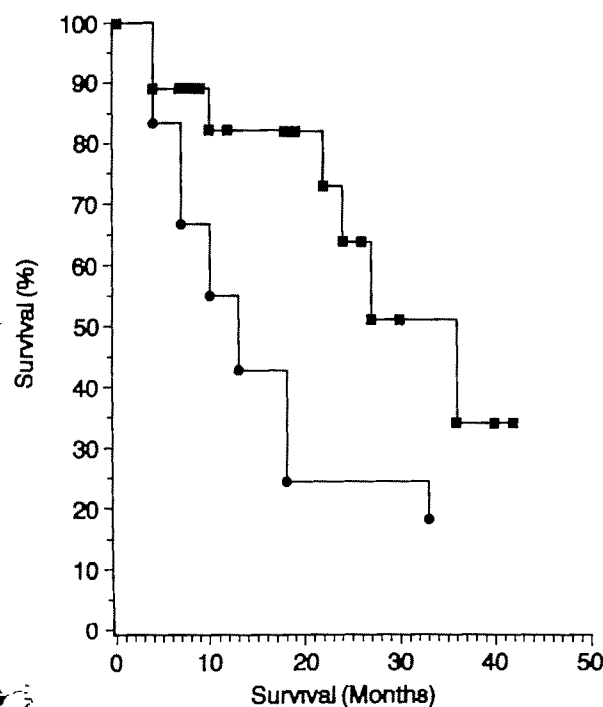


Fig. Results of cisplatin combination chemotherapy for elderly patients with urothelial tumours. ■: adjuvant chemotherapy for patients at high risk of relapse. ○: therapy for patients with metastatic disease.

Group 2 (metastatic disease)

Eighteen patients were included in this group, 7 (39%) with nodal disease and 11 (61%) with visceral metastasis. The majority (16 patients, 89%) had transitional cell carcinoma. Because their disease was progressing, their performance status was lower (median 2.0). The measured cardiac ejection fraction was $70\% \pm 7.4\%$ and creatinine clearance measured before chemotherapy was 67.6 ± 20.4 ml/min. Therapy was individualised, i.e. the end of therapy was planned to be at least 2 courses beyond complete remission after delivery of at least 7 courses. Therapy was terminated if disease progressed. In fact a median of 7 cycles per patient (range 2–9) was administered. Treatment was interrupted in 2 patients because of toxicity (severe nausea and vomiting) and 8 patients (44%) experienced infectious complications, all uneventful fever of unknown origin. Therapy resulted in renal impairment: the creatinine clearance rate dropped to 57.9 ± 17.5 ml/min ($P=0.06$) after therapy.

Seven patients (39%) achieved an objective response (5 CR, 2 PR) (Table); only 2 patients (11%) are alive and free of disease and 13 (72%) have succumbed to their disease, with a median survival of the whole group of 10.5 months (range 3–120+) (Fig.). Neither the dose intensity of cisplatin, the regimen used nor the tumour's histological type predicted the response to therapy.

Table Response Rate in Metastatic Disease

Site of metastases	No of patients	Clinical response		
		CR	PR	CR+PR
Nodes	7	2	0	2
Viscera	11	3	2	5
Total	18 (100%)	5 (28%)	2 (11%)	7 (39%)

CR = Complete response.
PR = Partial response.

Discussion

The proportion of cancer patients receiving potentially curative therapy declines with increasing chronological age (Samet *et al.*, 1986). Ageing is characterised by progressive functional deterioration which makes elderly patients less tolerant of chemotherapy than younger patients. Specifically, the risk of haemopoietic, mucosal, cardiac and neurological complications from aggressive chemotherapy increases with age, which encourages

physicians to reduce the dose level of chemotherapy administered to this population (Walsh *et al.*, 1989).

Since the introduction of cisplatin as treatment for patients with metastatic bladder cancer over a decade ago, the survival rate of patients with urothelial cancer has been slowly improving. A review of our experience with stage D bladder carcinoma during 1974 and 1975 showed a median survival of only 3 months (Samuels *et al.*, 1979). Today, using cisplatin combination chemotherapy, these same patients would achieve a median survival in excess of 3 years (Sternberg *et al.*, 1988). In the present analysis we evaluated whether a similar improvement has occurred with older patients.

To be valid, any statement regarding the use of cisplatin combination chemotherapy for metastatic urothelial cancer in elderly patients has to evaluate survival and quality of life. Since this was a retrospective analysis, we were unable to measure the latter factor. However, we did find that such aggressive treatment could be administered without treatment-related mortality to elderly patients who fulfilled the entry criteria.

Toxicity was significant. Treatment was discontinued in 6/36 patients (17%); in 3 cases this was because of gastrointestinal toxicity. Fourteen patients (39%) experienced a nadir sepsis, greater than has been reported previously for the younger urothelial cancer population treated with cisplatin combination chemotherapy (Sternberg *et al.*, 1988; Lo *et al.*, 1989).

The significant decrease in creatinine clearance rate was noteworthy. No patient, however, developed progressive renal insufficiency or required dialysis, results similar to those described for the M-VAC and CMV regimens. Such deterioration was expected in view of the progressive decline of glomerular filtration rate and tubular reabsorption with age (Balducci *et al.*, 1979). Hrushesky *et al.* (1984) failed to demonstrate that elderly patients had an increased risk of cisplatin nephrotoxicity, but their dosages were lower (60 mg/m²) than those used (70–100 mg/m²) in the present combinations, which also contained methotrexate, similarly associated with nephrotoxicity. The overall response rate of 39% for patients with metastatic disease is lower than that noted in our recent experience with CISCA (46%) and MVAC (65%). However, the overall survival of 10.5 months is comparable: 82 weeks for M-VAC and 40 weeks for CISCA regimens administered to patients with a mean age of 66 years (Logothetis *et al.*, 1990). These results indicate that for selected elderly patients with

advanced urothelial cancer, cisplatin combination treatment is effective and age should not exclude patients with metastatic disease from the potential benefit of such therapy.

The issue of adjuvant cisplatin combination chemotherapy for this patient population is less clear. Recent data suggested that adjuvant CISCA chemotherapy prolonged the disease-free survival of younger patients at high risk of recurrence (Logothetis *et al.*, 1988). Indeed, 44% of our 18 elderly patients are alive without evidence of disease with a median survival of 23 months, a result similar to our previous experience with adjuvant CISCA chemotherapy in bladder cancer. However, taking into consideration the toxicity (particularly the nephrotoxicity) associated with the treatment and the observation that neoadjuvant intravenous cisplatin plus radical radiotherapy can achieve a high remission rate and prolonged survival in elderly patients with high risk bladder cancer without causing excessive morbidity (Raghavan *et al.*, 1988), one must question whether aggressive adjuvant cisplatin combination chemotherapy is justified for elderly patients with urothelial tumours.

Cisplatin is the most active single agent against bladder cancer at the present time and probably represents the most important component of modern combination chemotherapy for urothelial tumours (Ackland and Vogelzang, 1988). The fact that M-VAC was shown to be more active than CISCA in a recent randomised study conducted at the M.D. Anderson Cancer Center, despite the higher doses of cisplatin in CISCA (100 mg/m²) than in M-VAC (70 mg/m²) (Logothetis *et al.*, 1990), indicates that such components as the other drugs and the schedule of administration are also important. The dose intensity methodology used by Hryniuk *et al.* (1987) (dosage of a therapeutic agent per unit of time) predicts the outcome in patients with a variety of haematological and solid tumours. In ovarian cancer, analysis of several combination chemotherapy regimens demonstrated that cisplatin was the only drug for which clinical response correlated with the dose intensity of an individual drug (Levin and Hryniuk, 1987). Based on that study, and because cisplatin is the only drug common to the 3 regimens, we analysed the actual delivery-dose intensity of cisplatin and found that in patients with metastatic disease dose intensity did not predict the outcome. However with decrease of tumour volume in patients at high risk of relapse, the dose intensity of adjuvant cisplatin did predict relapse. These data support the concept that an important cause of lessened benefit from chemo-

- therapy among elderly patients may be reduced dose intensity.

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Neo-adjuvant (Pre-emptive) Cisplatin Therapy in Invasive Transitional Cell Carcinoma of the Bladder

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Summary—Following 2 pilot studies which showed 57 and 61% response rates to intravenous cisplatin for transitional cell carcinoma of the bladder prior to definitive treatment, the West Midlands Urological Research Group (WMURG) and the Australian Bladder Cancer Study Group (ABCSG) independently began randomised trials to test the survival benefit of neo-adjuvant intravenous cisplatin prior to radiotherapy in T2–T4 M0 transitional cell carcinoma of the bladder.

Both trials failed to recruit their target numbers of 250 patients in the West Midlands and 320 in Australia. Since they had similar treatment protocols and eligibility criteria, they were combined in an overview analysis, achieving a total number of 255 patients.

Each treatment group was compared with its own control group and the differences were pooled to give an overall result. There was no difference in survival between treated and control patients. The odds ratio was 1.13 with the control groups faring marginally better than the chemotherapy groups. Even with 255 patients the 95% confidence interval of the odds ratio was wide (0.80–1.57). Although there is no clear evidence of a clinically worthwhile benefit from neo-adjuvant cisplatin, this approach must be tested in a larger study using combination treatments with greater activity in metastatic disease.

Developments in surgical and radiotherapy techniques for the treatment of localised muscle invasive bladder cancer have produced little improvement in overall survival. The presence of clinically undetectable metastatic disease at the time of presentation remains the principal cause of treatment failure (Skinner, 1980). Systemic chemotherapy that is effective in metastatic transitional cell carcinoma of the bladder may be combined with radical local treatment in the expectation that survival will be improved. The rationale for choosing a neo-adjuvant chemotherapy regime prior to radiotherapy has been outlined by Raghavan (1988).

Two pilot studies of neo-adjuvant cisplatin before radiotherapy for muscle invasive bladder cancer were carried out in the West Midlands (Fagg *et al.*,

1984) and in Australia (Raghavan *et al.*, 1985) which both demonstrated that cisplatin was active in locally advanced bladder cancer, producing objective response rates of the primary tumour of 61 and 57%. The toxicity was acceptable in both studies. Both centres independently embarked on randomised trials to determine if neo-adjuvant cisplatin conferred a survival benefit when used prior to radical radiotherapy. The West Midlands trial aimed to recruit 250 patients and the Australian study 320 patients in order to provide a good chance of detecting differences in 5-year survival of 20% or more. Neither trial was of adequate size to detect reliably the smaller differences of 10 to 15% that are now considered worthwhile (Hall, personal communication). Both trials failed to recruit their target numbers and were closed early for reasons that have been discussed elsewhere (Raghavan, 1988). In order to obtain the most valid and reliable result from these small studies, the trial co-

ordinators decided to combine them in an "overview" analysis, rather than publishing each separately, since the treatment protocols and eligibility criteria were very similar. However, in an "overview" analysis the difference between the observed and the expected numbers of deaths is calculated within each trial and then pooled for a statistical test. Since each group is compared with its own control group, minor differences in patient characteristics do not bias the result (Henderson *et al.*, 1988). The "overview" analysis has the advantage that the maximum amount of information about any treatment difference has been used, increasing the reliability of the results that are obtained.

Patients and Methods

Selection of patients

In the West Midlands study 159 patients were entered between June 1984 and June 1988 from 10 hospitals; in the Australian study 96 patients were entered between February 1985 and February 1988 from 10 centres in New South Wales and Victoria. All patients had biopsy proven, muscle invasive transitional cell carcinoma of the bladder category T2-T4 NX M0. In Australia, T2 patients were included only from July 1986. Patients with glandular or squamous elements were included but pure squamous or adenocarcinomas were excluded. Patients with prior malignant tumours other than non-melanomatous skin cancer were excluded. Performance status had to be greater than 50% of normal activity (ECOG 0-3 or WHO 0-2). In the Australian study the serum creatinine had to be less than $1.75 \times$ upper limit of normal and in the West Midlands study creatinine clearance had to be over 50 ml/min. An upper age limit of 75 years was applied in the West Midlands study and the Australian study had an upper age limit of 80 years. All patients in both studies gave informed consent.

Patients were randomised by telephone call to the respective trials office to receive either cisplatin before radical radiotherapy or radical radiotherapy alone. In the West Midlands trial, randomisation was carried out with stratification by centre and T category of disease. The Australian patients were randomised without stratification.

Chemotherapy

Patients received cisplatin at a dose of 100 mg/m² by intravenous infusion following hydration and anti-emetics; this was repeated at 3-weekly intervals. In the West Midlands study patients were

scheduled to receive 3 courses and in the Australian study 2 courses before commencing radiotherapy. Dosage was reduced to 80 mg/m² if the creatinine exceeded $1.5 \times$ upper limit of normal in Australia and reduced to 50 mg/m² if creatinine clearance fell to 40-50 ml/min in the West Midlands. Cisplatin was withheld in both studies if myelosuppression occurred (WCC < 2500 μ m in West Midlands and < 3000 μ m in Australia; platelets $\leq$ 100,000/l in both studies).

Radiotherapy

Radiotherapy was started within 3 weeks of completing the last course of chemotherapy in the West Midlands and approximately 10 days after completing the last course of chemotherapy in Australia. In the West Midlands study the treatment volume was the target volume (bladder plus tumour) plus a 1 cm margin in all dimensions except inferiorly, using anterior and 2 posterior oblique fields and an 8 Mev linear accelerator. A 6500 cGy modal dose was given in 30 daily fractions within 6 weeks. In the Australian study 4500-5000 cGy was given to the whole pelvis in 200 cGy fractions using 4-8 Mev linear accelerators and a 3 or 4 field box technique. A further boost of 1000-1500 cGy to the bladder was then given and treatment scheduled to be completed in 6 weeks. In both studies planning was either by computed axial tomography or by cystography according to availability in Australia and randomisation in the West Midlands.

Follow-up

In both studies patients were followed up by cystoscopy and examination under anaesthesia every 3 months for the first year, 6-monthly for the next 2 years and annually thereafter until death. Biopsies were taken at the discretion of the participating surgeon. Where appropriate salvage cystectomy was performed.

Statistical analysis

Patient measurements were compared between groups using the Mann-Whitney U test and categorical data were compared using Pearson's χ^2 test.

The duration of survival has been used as the principal criterion of response. The analysis of survival includes all randomised patients in the groups to which they were allocated. Survival was censored at 31 January 1989, when the status of all patients was known with certainty. Survival curves were drawn using the method of Kaplan and Meier (1958) and the significance of the differences

between curves assessed using the log rank χ^2 test (Peto *et al.*, 1977). Each trial was analysed separately in this way and the results were then pooled to form an overview analysis. In each trial the difference has been calculated between the number of deaths observed among the treated patients (O) and the number expected (E) on the assumption of no treatment effect. (O-E) is negative if the treated group fares better than the controls and positive if it fares worse. If the treatment has no effect, then each of the (O-E)s could equally be positive or negative and their sum will differ from zero only by chance. If the treatment reduces mortality, then the (O-E)s will tend to be negative and this effect may clearly stand out when the grand total of the (O-E)s is calculated (Henderson *et al.*, 1988).

Results

Patients analysed

In the West Midlands study 83 patients were randomised to receive neo-adjuvant cisplatin and

76 to radiotherapy alone. In the Australian study the numbers randomised were 42 and 54 respectively. The median follow-up was 16 months (range 1-56) and the patient characteristics are summarised in Table 1.

Within each trial, the 2 treatment groups were well balanced for all characteristics, except for T category in the Australian study. The excess of T3 patients in the treated group is explained by the use of an unstratified, unblocked randomisation with the trial closing early and the late inclusion of T2 patients into the trial from July 1986.

As expected from the eligibility criteria, the Australian patients were slightly older. They also had slightly worse performance status, higher T category and less hydronephrosis. The 2 trials were comparable in terms of their sex ratio, haematological and biochemical measurements.

Chemotherapy

The chemotherapy received in each trial is shown in Table 2. Of the 125 patients randomised to receive chemotherapy, 110 (88%) completed 2

Table 1 Details of Patients

a. Groups		West Midlands				Australia				χ_1^2	P
		Control (N=76)		Treated (N=83)		Control (N=54)		Treated (N=42)			
		N	%	N	%	N	%	N	%		
Sex											
	Male	61	80	64	77	45	83	32	76	0.1	0.76
	Female	15	20	19	23	9	17	10	24		
T category											
	T2	24	32	26	31	14	26	3	7	5.8	0.05
	T3	41	54	44	53	27	50	34	81		
	T4	11	14	13	16	13	24	5	12		
Performance status											
	0	68	89	71	86	42	78	33	79	3.0	0.09
	1	7	9	12	14	12	22	8	19		
	2	1	2	0	0	0	0	1	2		
Hydronephrosis											
	None	57	75	54	65	43	80	35	83	4.0	0.04
	Unilateral	18	24	26	31	10	19	7	17		
	Bilateral	1	1	3	4	1	1	0	0		
b. Measurements		Control (N=76)		Treated (N=83)		Control (N=54)		Treated (N=42)			
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	P	
	Age	65	6.8	65	6.6	65	6.5	68	8.0	0.07	
	Creatinine	0.1	0.02	0.1	0.02	0.1	0.03	0.1	0.02	0.12	
	Haemoglobin	13.6	1.8	13.3	2.3	13.6	1.5	13.4	1.7	0.56	
	White cell count	8.9	3.6	8.3	2.6	8.7	2.7	8.8	2.8	0.21	
	Platelets	317	104	327	115	307	103	329	115	0.95	

Table 2 Courses of Chemotherapy

	<i>West Midlands</i> (<i>N</i> = 83)		<i>Australia</i> (<i>N</i> = 42)		<i>Both trials</i> (<i>N</i> = 125)	
	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)
First course						
Full	67	(81)	40	(96)	107	(86)
Reduced	9	(11)	1	(2)	10	(8)
None	7	(8)	1	(2)	8	(6)
Second course						
Full	66	(80)	37	(88)	103	(82)
Reduced	6	(7)	1	(2)	7	(6)
None	11	(13)	4	(10)	15	(12)
Third course						
Full	62	(75)				
Reduced	8	(10)				
None	13	(15)				

courses. Eight patients (6%) received no chemotherapy; 4 refused, 3 were judged to be too ill, although they fulfilled the entry criteria when randomised, and 1 West Midlands patient had a non-invasive tumour on pathological review. Seven patients (6%) received only 1 course of chemotherapy. In this group early death (4 patients), progression of disease (1 patient), toxicity (1 patient) and severe nausea (1 patient) were the reasons given for stopping treatment. Four West Midlands patients (3%) did not receive their third cycle of cisplatin as a result of reduced creatinine clearance (2 patients), nausea (1) and myelosuppression (1). Of the 117 patients who started treatment, 92 (79%) completed their given cycles without dose modification. The commonest reason for dose modification was renal dysfunction in 15 patients.

Radiotherapy

Of the 255 patients in the studies, 226 (89%) received the full radiotherapy treatment (Table 3).

Table 3 Deviations from Radiotherapy Protocol

<i>Reason</i>	<i>Radiotherapy reduced</i>	<i>Radiotherapy not given</i>
Progression	12	7
Radiation cystitis	2	0
Renal failure	2	0
Anaemia	1	0
Thrombocytopenia	1	0
Previous radiotherapy	0	1
Radiotherapy not to protocol	1	0
Ineligible patients	0	2
Total	19	10

Ten patients (4%) received no radiotherapy; 7 because of disease progression, 1 because previous pelvic radiotherapy had been given and 2 who were withdrawn before chemotherapy (see above). Nineteen patients (7%) received a reduced dose of radiotherapy; in 7 cases this was due to progression of disease, 5 patients died before treatment was completed, 1 was treated at another centre (3400 cGy in 6 fractions) and 6 patients had side effects. The median modified dose received by these 19 patients was 3300 cGy (range 300–6100).

Survival

The survival curves for both trials are shown in Figure 1 and survival stratified by T category is shown in Figure 2. There was no significant difference in survival between treated and control patients in either trial. In the West Midlands trial there were 46 deaths in the 83 patients treated with neo-adjuvant cisplatin and 41 deaths in the 76 patients treated with radiotherapy alone ($\chi^2 = 0.06$, $P = 0.81$). In the Australian trial there were 25 deaths in the 42 patients in the neo-adjuvant cisplatin arm and 26 deaths in the 54 patients in the radiotherapy arm ($\chi^2 = 0.68$, $P = 0.41$). The median survival times are shown in Table 4. Although the (O–E)s were in favour of the control group in both trials (*i.e.* 2.91 and 1.13), there was no significant difference between the treatment groups in the overview analysis (Pooled (O–E) = 4.04, $\chi^2 = 0.48$, $P = 0.49$). The odds ratio was 1.13 (95% confidence interval 0.80–1.57).

Given the wide confidence interval for differences in survival based on the data as a whole, it is clear that there is inadequate information for subgroup analyses. However, differences in the effect of treatment have been suggested in various subgroups by a number of workers. In our trials there was no significant difference in the effect of chemotherapy when comparing those above and below the medians for age, creatinine, haemoglobin and white cell counts, nor was any difference seen when comparing males and females, performance status 0 with 1 and 2, or those without hydronephrosis with those with unilateral and bilateral hydronephrosis. There were no significant differences in survival between centres.

Discussion

It has been proposed that a significant improvement in survival of patients with invasive bladder cancer will be achieved by the introduction of systemic therapy that is capable of complete clearance of

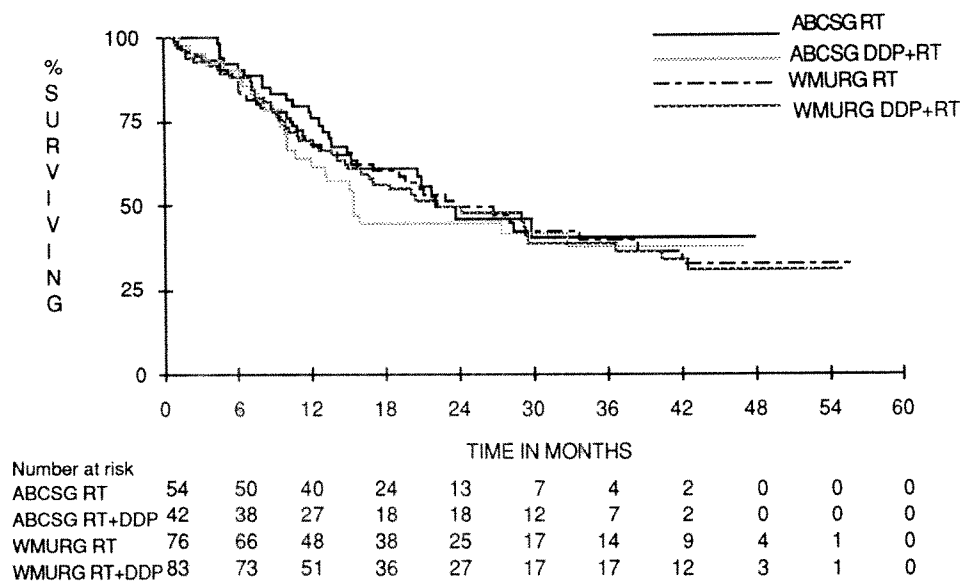


Fig. 1 Survival curves for each treatment group by centre.

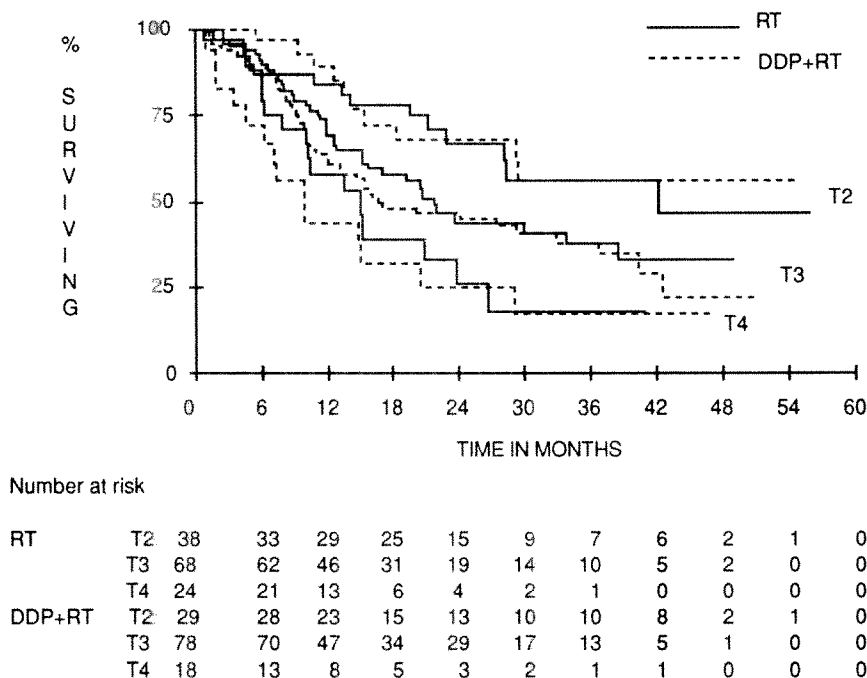


Fig. 2 Survival curves stratified by treatment and T category.

microscopic metastases in a high proportion of cases. The optimal definitive treatment (radiotherapy or cystectomy) remains the subject of controversy. Cisplatin was chosen for pilot studies by the 2 groups because it had the highest response rate of the single agents and combination chemotherapy

regimens did not appear, at that time, to have a significant advantage (Yagoda, 1982). There is now some evidence that combination chemotherapy may produce a survival advantage over single agent cisplatin (Loehrer *et al.*, 1990), although 4 previous studies showed no clear benefit (Soloway *et al.*,

Table 4 Summary of Survival Analysis

	West Midlands			Australia		
	Median (months)	3-year survival	CI	Median (months)	3-year survival	CI
Overall	24	40%	30-49	22	40%	28-52
Treated	24	39%	26-52	15	38%	21-54
Control	24	40%	27-53	22	41%	24-58
Odds ratio	1.05		0.69-1.61	1.36		0.72-2.21
χ^2	0.06			0.68		
P	0.81			0.41		

1983; Khandeker *et al.*, 1985; Troner *et al.*, 1987; Hillcoat *et al.*, 1989). Responses in the 2 pilot studies were assessed using cystoscopy, biopsy, examination under anaesthesia and CT scanning. Because of the limitations of these methods of assessing the primary tumour, complete and partial objective responses defined by WHO criteria were combined to give an overall response rate. It was thought at that time that the response rates of 57 and 61% indicated that neo-adjuvant cisplatin might confer a survival advantage for locally advanced transitional cell carcinomas of the bladder when used before radical radiotherapy. If the survival advantage was 20 to 25%, a randomised controlled trial of 250 to 320 patients would have a good chance of demonstrating this advantage. In both centres a 20 to 25% improvement in survival was considered clinically worthwhile and it was believed that a recruitment of 250 to 320 patients was a practical proposition. The recent postal survey of urologists, radiotherapists and oncologists in the EORTC genitourinary group and urologists in the United Kingdom carried out by Hall (personal communication) has shown that clinicians now consider that a 10 to 15% survival benefit due to chemotherapy is worthwhile and would make them alter their management of invasive bladder cancer. Therefore, trials must now be designed which aim to recruit much larger numbers than our studies.

Both studies failed to reach their recruitment targets. In Australia recruitment fell off sharply following the first reports of the results of M-VAC (Sternberg *et al.*, 1985) and the development of nerve-sparing techniques of radical cystectomy. In the West Midlands recruitment was steady during the 4 years of the trial but some centres did not enter patients because they were unable to comply with the radiotherapy requirements of the protocol. The West Midlands protocol required CT scanning

at a time when many hospitals did not have this available for planning. The treatment regimen was also one that was not routinely used by all radiotherapists. Thus many patients were excluded because the trial protocol did not allow for the diversity in planning and treatment that were practised. If recruitment targets for large trials are to be met, then protocols must represent current practice in the standard treatment arm. If there is diversity in the standard practice without appreciably different results, protocols must allow for this.

Neither trial group was aware of the other's trial until the Australian study was closed to further recruitment at the beginning of 1988. The protocols and patient characteristics were compared to see if there were any major differences between the 2 trials. Despite minor differences in the protocols with regard to age and renal function, the patient characteristics differed only slightly. The major difference between the 2 protocols was in the number of courses of cisplatin given. Although the response rate increases with further courses of cisplatin, the increased response for the third course is small and offset by greater toxicity. There may also be an effect from delaying the start of radiotherapy by a further 3 weeks, but this cannot be evaluated from the present studies. Cisplatin was well tolerated and did not present problems with administration in the context of a large multicentre trial; 12% did not receive a second course of cisplatin, which is comparable to the 13% who did not receive preliminary chemotherapy in the study reported by Shearer *et al.* (1988) and 18% reported by McCullough *et al.* (1989); 85% of the West Midlands patients received a third course with 10% having a reduced dose. Neither study attempted any maintenance chemotherapy, which was attempted by both Shearer *et al.* (1988) and McCullough *et al.* (1989), with only 59 and 41% receiving their maintenance chemotherapy. Long

courses of adjuvant chemotherapy cannot be given to the majority of patients with invasive bladder cancer. The main reasons for not receiving the full course of radiotherapy was progression of disease. Although there was little difference between the 2 treatment arms, the radiotherapy was delayed by the cisplatin for 6 to 9 weeks, which may have allowed more time for metastatic disease to manifest itself.

The 3-year survival rate of 39% for patients with T3 tumours in our studies is the same as reported by Shearer *et al.* (1988) using adjuvant methotrexate and by Richards *et al.* (1983) for adjuvant doxorubicin and 5-fluorouracil. These figures are also similar to the 3-year survival of 45% for patients treated by pre-operative radiotherapy and cystectomy and 33% for patients treated by radiotherapy in the trial reported by Bloom *et al.* (1982) for T3 tumours recruited from 1966 to 1975. The consistency of these results implies that there has been no major change in selection or staging of patients for these trials.

Although the control group had a marginally better survival in our trials, the small numbers of patients have led to a wide confidence interval; thus the results are also compatible with a reduction attributable to chemotherapy of up to 20% in the odds of death. This is equivalent to a 12% improvement in survival at 3 years from 40% to 52%. Conversely, the results are compatible with an increase in the odds of death of 57%, equivalent to a 34% reduction in survival at 3 years from 40% to 6%. Clinical trials that are too small may be misleading, some showing an apparently significant benefit of treatment and some showing no significant benefit for the same treatment. An individual study may, by chance, demonstrate a beneficial effect when there is no real advantage or even a disadvantage. If a number of small trials show no significant advantage, this may conceal a small survival benefit since their results may all point in the same direction. The significance of a small survival benefit may be shown by combining a number of small trials in an overview analysis.

The present work has shown that it is productive to combine studies. Despite the ethnic, cultural and geographical differences between the 2 populations treated in our trials, the results are remarkably consistent and by combining these studies, the reliability of the result has been improved. However, the confidence interval is wide and a larger number of patients is needed to exclude the possibility of a 10 to 15% survival difference. Neither centre was able to answer the question

posed by the trial, even given the most optimistic result for the benefit of chemotherapy. Even the combined study does not have the statistical power required to exclude a 10 to 15% benefit for chemotherapy. Thus, if we are to test the value of the introduction of neo-adjuvant chemotherapy in the standard management of muscle invasive bladder cancer, large multinational clinical trials must be completed.

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Comparison of Transrectal Ultrasound and Magnetic Resonance Imaging in the Staging of Prostate Cancer

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Summary—A group of 32 patients with a histological diagnosis of prostate cancer underwent transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) to stage the disease. TRUS was more sensitive in the detection of tumour and in the detection of direct extracapsular spread. MRI was more sensitive in the detection of tumour involvement of the seminal vesicles and bladder base. MRI allowed the detection of lymphadenopathy and bone metastases in the lumbosacral spine and pelvis. During MRI the short tau inversion recovery (STIR) sequence was found to be particularly useful for the detection of tumour spread. TRUS and MRI are complementary investigations and for the accurate staging of prostatic malignancy both investigations should be used.

In most parts of the world prostate cancer is the second or third most frequent tumour in males, with annual death rates varying from 2 (Japanese males in Japan) to 24 (US negroes) per 100,000 (Wynder *et al.*, 1971). The annual incidence in England and Wales is greater than 7000. At present 60 to 75% of patients present with locally advanced or metastatic disease and treatment is therefore palliative (Boxer, 1977; Murphy, 1982). Curative treatment, in the form of radical radiotherapy or radical retropubic prostatectomy, is possible when the disease is confined to the prostate. The main cause of failure to eradicate prostatic carcinoma completely in patients with apparently localised tumours is the inability before surgery to recognise (1) local extension of the neoplasm beyond the gland and (2) pelvic nodal metastases. Selection of patients is therefore very important and depends heavily on the accuracy of pre-operative staging.

The time-honoured method for staging the primary lesion has been digital rectal examination. This has been shown to be inaccurate (Fair and Kadmon, 1983; Spigelman *et al.*, 1986). Transrectal

ultrasound has allowed detailed examination of the prostate. The more recently developed high frequency transducers allow differentiation of the internal zonal anatomy of the gland and the high resolution obtained permits the identification of tumours as small as 4 mm in diameter (Shinohara *et al.*, 1991). TRUS is accurate in the staging of prostate cancer in 85 to 90% of cases (Salo *et al.*, 1987; Andriole *et al.*, 1988). Magnetic resonance imaging provides accurate anatomical detail and allows some degree of tissue differentiation. It has proved disappointing in the diagnosis of prostatic disease but in known cases of prostatic carcinoma accuracy rates for staging of 83 to 89% have been claimed (Ling *et al.*, 1986; Biondetti *et al.*, 1987; Hricak *et al.*, 1987). Computed tomography (CT) provides excellent anatomical detail but tissue differentiation in the pelvis is poor. When compared with the other methods of staging the primary tumour, CT is accurate in only 58 to 65% of cases (Hricak *et al.*, 1987; Platt *et al.*, 1987; Demas, 1988).

The Bristol experience of MRI of the prostate extends to over 100 cases. It includes the routine use of the short tau inversion recovery (STIR) sequence which has been available only in recent years and has not been used in some of the earlier

reports mentioned above. The aim of the present report was to compare TRUS and MRI in the evaluation of the malignant prostate and to define more accurately the relative roles of the 2 investigations in clinical practice.

Patients and Methods

Thirty-two consecutive patients with a histological diagnosis of prostatic carcinoma were studied. Each patient underwent TRUS and MRI examination of the prostate within a period of 1 month. Transrectal ultrasound was performed using a Bruel and Kjaer 8551 7MHz multiplaner probe. For some patients, such as those with rectal involvement, the rotating transducer (Bruel and Kjaer 1850) was used. All ultrasound examinations were performed by the same operator (D.C.). Two patients, one of whom had an extensive prostatic carcinoma involving the rectum, were unable to tolerate the examination.

Magnetic resonance imaging was performed on a Picker Vista HP 2055 0.5 tesla machine. Each scan took approximately 45 min to perform, the duration depending on the number of sequences used. All scans were performed using T1-weighted sagittal views together with T2-weighted and proton-density transverse views. In addition, STIR sequences in the transverse plane were used. T1-weighted coronal and sagittal STIR sequences were used in 2 patients; 1 patient was unable to tolerate the examination as a result of claustrophobia.

The hard-copy films of both the TRUS and the MRI examinations were reported in isolation by the 2 primary authors (D.C. and M.C.). Prostate cancer was seen as a hypoechoic area on TRUS except in 1 patient where the tumour was hyperechoic. The integrity of the capsule and seminal vesicles was examined. During magnetic resonance imaging the following abnormalities were noted: an area of signal change within the prostate corresponding to tumour; loss of continuity of the periprostatic venous plexus on the anterior and

lateral surfaces of the gland corresponding to capsular breach (Poon *et al.*, 1988); evidence of tumour, and in particular areas of signal change, within the seminal vesicles, bladder base and the adjacent levator ani musculature; evidence of metastatic spread to adjacent tissues, lymph nodes and bone.

Results

In all, 32 patients were examined. Tumour stage as assessed by the various modalities is summarised in Table 1. Compared with the radiological findings, clinical examination understaged the tumour in 7 cases and overstaged it in 4.

Two patients, 1 of whom had an extensive carcinoma invading the rectum, were unable to tolerate the ultrasound probe. One patient was unable to tolerate the MRI examination as a result of claustrophobia; 29 patients were therefore available for direct comparison of the 2 imaging techniques. The radiological findings are summarised in Table 2.

Tumour was visible in 27 cases using TRUS and 20 of these had evidence of capsular breach (Figs 1 and 2). MRI detected tumour in 24 cases with capsular breach in 15. Invasion of seminal vesicles was seen in 7 cases using MRI and in only 1 on TRUS. Bladder base invasion was seen in 4 cases on MRI and in 1 using TRUS. Four patients had lymphadenopathy on MRI. The enlarged nodes were in the obturator, iliac and para-aortic regions. MRI detected bone metastases in 6 patients. The routine pelvic scan allows assessment of the pelvic bones together with the vertebrae below the level of L3.

Table 1 Staging of 32 Patients with Prostate Cancer by Clinical Examination, TRUS and MRI

Stage	Clinical	TRUS	MRI
T1, 2	14	7	5
T3	12	21	23
T4	6	2	3
Total	32	30	31

Table 2 Radiological Findings in 29 Patients with Carcinoma of Prostate

	TRUS	MRI
Tumour visible	27	24
Capsular breach	20	15*
Seminal vesicle involvement	1	7†
Tumour invasion of bladder	1	4
Tumour invasion of rectum	2	2
Lymphadenopathy		4
Bone metastases		6

* One patient had bilateral breach on MRI and unilateral breach on TRUS

† Seminal vesicle involvement unilateral in 4 cases, bilateral in 3.



Fig. 1 Transrectal ultrasound scan in the transverse plane of a prostate containing a localised carcinoma.

Discussion

These data illustrate the importance of TRUS in the detection of carcinoma of the prostate and particularly in the visualisation of direct capsular breach. Ultrasound appears to be superior to MRI in this respect, for 20 patients with capsular breach were detected on TRUS, whereas MRI detected only 15. In the detection of seminal vesicle involvement MRI seems to be more sensitive. Of 7 patients with radiological evidence of tumour extension into the seminal vesicles TRUS detected only 1. Tumour involvement of the seminal vesicles was noted only if there was a signal change in those structures (Fig. 3). The normal seminal vesicle produces a very high signal on a T2-weighted or a STIR image. These 2 sequences were found to be important in assessing the seminal vesicles. The STIR sequence is a technique that suppresses signal from fat and in contrast increases signal from areas of high water content. The seminal vesicles have a very high signal and tumour has a relatively lower signal (Fig. 4). This is in contrast to tumour shown by STIR in other parts of the body where, relative to the low signal of surrounding tissues, the tumour has a high signal. On the T2 transverse image MRI allows visualisation of the neurovascular bundles on the posterolateral surfaces of the prostate. This is of particular importance to the

surgeon planning a nerve-sparing radical retropubic prostatectomy.

The superiority of TRUS over MRI in the detection of intraglandular tumour and direct extracapsular spread is in agreement with a previous report by Friedman *et al.* (1988). This review, together with the data reported by Bezzi *et al.* (1988), also emphasises the sensitivity of MRI in the detection of tumour involvement of the seminal vesicles. It is probable that TRUS is inadequate in this respect and it is important therefore that, in cases where accurate staging is required (such as patients being staged prior to radical prostatectomy), both investigations are used.

Tumour invasion of the bladder occurred in 4 cases. In only 1 case was this detected using TRUS. Tumour invasion of the rectum by prostatic carcinoma can be imaged by either method. However, some patients with rectal involvement find it difficult to tolerate an ultrasound probe. In this situation the axial-scanning probe (Brüel and Kjaer 1850) is more easily tolerated than the multiplanar probe (Brüel and Kjaer 8551) because of the narrower shaft. In addition, the rotating transducer provides better images in the case of encroachment of tumour into the rectum because a 360° view is obtained. There were 3 cases of rectal involvement in the series. All 3 patients had MRI which clearly showed the tumour. Only 2 underwent



Fig. 2 Transrectal ultrasound scan in the transverse plane of a prostatic carcinoma. There is capsular breach anteriorly.

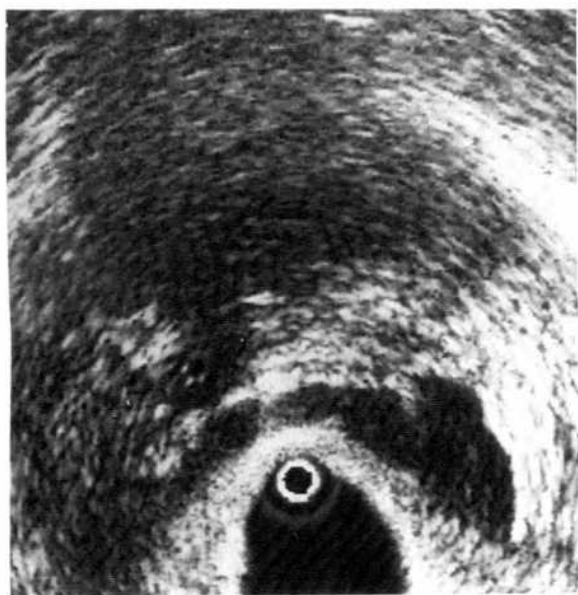


Fig. 3 Transrectal ultrasound scan in the transverse plane of the seminal vesicles. There is distortion of the right seminal vesicle due to invasion by tumour.

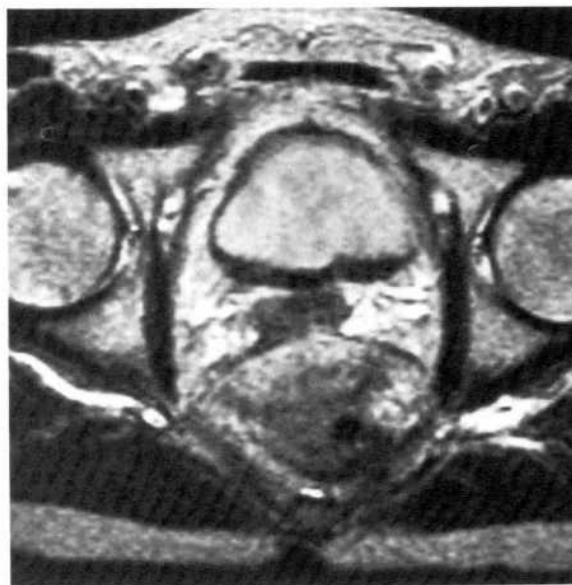


Fig. 4 Transverse, T2-weighted MRI scan showing abnormally low signal in the right seminal vesicle as a result of tumour invasion.

TRUS because the third was unable to tolerate even the smaller of the 2 ultrasound probes.

Four patients had lymphadenopathy on MRI. The presence of enlarged lymph nodes is not diagnostic of nodal metastases. As with CT scanning, the size of the nodes is taken to be an indicator of the likelihood of metastatic disease (Fig. 5). A lymph node exceeding 1 cm in diameter is very likely to be involved by tumour. MRI does, however, allow a degree of tissue differentiation and this, combined with flow effects, allows MRI to distinguish lymph nodes from the adjacent large vessels. The signal intensity of the lymph nodes has not been shown to be helpful and MRI has not been able to find tumour in normal sized nodes (Sawczuk *et al.*, 1983; Wiener *et al.*, 1986; Schnall *et al.*, 1990). Bezzi *et al.* (1988) reported 69% accuracy and 95% specificity in detecting lymph node metastases. These figures are similar to those reported for CT. No lymph nodes were detected using TRUS.

Six patients had bone metastases on MRI. Only metastases below the level of the third lumbar vertebra can be imaged with a routine pelvic scan but it is of interest that every patient with a positive isotope bone scan had bony deposits on MRI of the pelvis. This is a reflection on the distribution of bone metastases in prostate cancer and the sensitivity of MRI in their detection.

Review of the MRI films allowed assessment of which views and sequences gave the most useful diagnostic information. The T2 transverse scan allows evaluation of the internal architecture of the gland, showing clearly the central and peripheral



Fig. 5 Transverse MRI scan (STIR sequence) showing abnormally high signal in the right pelvic lymph node. This is strongly suggestive of metastatic invasion.

zones together with abnormal low-signal areas suspicious of tumour. In addition, it shows clearly the capsule, the surrounding high signal periprostatic venous plexus and the seminal vesicles. The T1 coronal view provides further assessment of the integrity of the prostatic capsule together with excellent imaging of the pelvic lymph nodes. Both of these sequences provide information on the state of the pelvic bones. Scanning in the sagittal plane provides little additional diagnostic information concerning the prostate, seminal vesicles and pelvic nodes. However, the T1 sagittal scan allows assessment of the lower lumbar and sacral vertebrae with metastatic deposits showing as low signal areas within the bone (Fig. 6). A single mid-sagittal scan, such as the "pilot" for the T1 coronal views, probably provides sufficient information. The STIR sequence frequently provides additional diagnostic detail. In this series it provided additional information concerning capsular breach and tumour involvement of the seminal vesicles and lymph nodes in 5 cases. In a further 4 cases it provided confirmation of such changes suspected from the conventional spin echo sequences. Using only those sequences which give the maximum information, the scanning time can be kept to a minimum. The total scanning time on our machine of the T2 and STIR transverse views plus the T1 coronal sequence, including the mid-sagittal "pilot", is less than 30 min.



Fig. 6 Sagittal, T1-weighted MRI scan showing metastatic deposits in the lumbosacral spine.

When considering the relative merits of the 2 investigations, factors such as cost, time and availability have to be taken into account. TRUS is cheap and more readily available. The examination takes about 15 min. It has the advantage of allowing immediate guided biopsy via the transrectal route. MRI is expensive, the current cost of a pelvic scan in Bristol being £175. As outlined above, the scanning time varies from 30 to 60 min, depending on the number of sequences used. Biopsy under MRI guidance has been performed but is more difficult than biopsy using ultrasound control. Acceptability by patients of both procedures is good. Relatively few patients are unable to tolerate the ultrasound probe. Those with extensive tumours involving the rectum generally find the examination particularly uncomfortable. Claustrophobia during MRI scanning is occasionally a problem but only a few patients are unable to tolerate the examination for an adequate length of time.

In conclusion, the roles of TRUs and MRI in the staging of carcinoma of prostate are complementary. In our opinion the patient should be examined first by TRUS. If there is the slightest doubt concerning the extent of the tumour or if the patient is a candidate for curative surgery, MRI will provide additional information on the status of the seminal vesicles, pelvic lymph nodes and the bones of the lumbosacral spine and pelvis.

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Prognostic Value of Raised Prostatic Acid Phosphatase and Negative Skeletal Scintigraphy in Prostatic Cancer

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Summary—Of 438 consecutive cases of newly diagnosed prostate cancer, 178 (41%) had skeletal metastases (T0-4 M1) at the time of diagnosis according to skeletal scintigraphy; 139 men had serum prostatic acid phosphatase (PAP) greater than twice the upper limit of normal on 2 separate occasions at the time of diagnosis and 65% of them had metastases on bone scan. However, 49 men with normal bone scans were found to have similarly raised serum PAP. (Such patients are defined as having skeletal metastases in the current Medical Research Council immediate versus deferred orchiectomy study and stratified accordingly). The actuarial survival of this group was calculated by life table methods and was compared with that of 2 other subgroups: those patients having metastases demonstrated on bone scan, and those patients having both normal bone scans and normal serum PAP.

The survival of the "metastatic by acid phosphatase" group was significantly better than that of the "metastatic by bone scan" group but did not differ from that of patients having both normal scans and PAP.

For patients with no scintigraphic evidence of skeletal metastases at diagnosis, those with a raised PAP were at a significantly greater risk of scan conversion, although this was more powerfully predicted by high histological grade.

The diagnostic value of prostate cancer tumour markers has been studied closely over recent years, largely as a result of the introduction of prostate specific antigen, which has invited comparison with more established tumour markers. Less attention has been given to the prognostic value of the level of these markers at the time of diagnosis. There is evidence to suggest that circulating levels of both PAP and prostate specific antigen (PSA) correlate positively with tumour stage (Stamey *et al.*, 1987) and thus it might be assumed that raised levels measured at the time of diagnosis imply a poorer prognosis, since tumour stage alone is a good indicator of prognosis. There is, however, some reason to question this assumption since the elaboration of enzymes is a normal function of the prostatic cell, and this ability may be lost in poorly differentiated tumours. Marked variation in the

synthesis of PAP by metastatic prostate cancer cells has been demonstrated using immunohistochemical methods (Keillor and Aterman, 1987). This mechanism has been suggested to explain the observation that some patients die of widespread metastatic prostate cancer, without significant elevation of serum PAP (Bruce and Choe, 1987).

The prognostic value of skeletal scintigraphy is established (Merrick *et al.*, 1985). The prognostic significance for patients with an elevated serum PAP and a normal bone scan at the time of presentation is less clear. We have therefore studied a group of such patients and compared their survival with that of patients with positive bone scan at presentation and that of those with both normal PAP and bone scan.

Patients and Methods

Between January 1978 and September 1988 there were 438 consecutive new cases of histologically

confirmed carcinoma of the prostate in the University Department of Surgery (WGH) and Department of Urology at the Western General Hospital in Edinburgh. They have been followed up regularly as described previously (Goodman *et al.*, 1988). All were primary referrals, with patients diagnosed elsewhere and subsequently followed up in this department over the same period being excluded from the analysis. A further 5 patients with atypical tumours, either "endometrioid" or papillary carcinoma of the prostate, and 9 patients with a clinical picture of advanced prostate cancer in whom histological confirmation proved impossible before death, are also excluded.

Serum prostatic acid phosphatase was measured by enzymatic methods early in the series and by radioimmunoassay since 1982. Thus the "normal range" was not constant throughout the study. An elevated level is defined here as twice the upper limit of the normal range current at the time of diagnosis. Blood samples were drawn before clinical examination or instrumentation and, when elevated, second samples were taken at least 48 h after the first and before initiation of any specific treatment. Skeletal scintigraphy was performed and interpreted as previously described (Merrick *et al.*, 1985). Survival probabilities based on partially censored observations were calculated by life table methods and the significance of differences between survival in various subgroups was estimated by the log rank method (Peto *et al.*, 1977). Expected survival was calculated for each patient in the series by reference to current life tables for Scottish males for the year of presentation (Annual Reports of the Registrar General for Scotland, 1978-1988). The expected survival in the group is derived by summation of the individual probabilities of all men in the group.

Results

Follow-up either to date or death ranged from 20 days (the earliest death) to 10.7 years (mean 2.77 years); 67 men remained at risk at 5 years. The mean age of the group was 72.5 years (range 45-91.0).

Of the 438 men, 178 (41%) had skeletal metastases diagnosed by bone scan. Of the remainder, 6 patients had equivocal bone scans; 254 patients had negative scans and 49 of these (11% of all patients) had serum PAP greater than twice the upper limit of normal on 2 occasions at the time of diagnosis.

Survival of all patients (calculated by life table methods, of deaths due to all causes) grouped on the basis of scintigraphic findings alone is shown in Figure 1. (The 6 patients with equivocal findings are grouped together with those having negative scans). Expected survival of the entire group at 5 years is superimposed for comparison.

The survival of all patients in the series grouped on the basis of serum PAP at the time of diagnosis is shown in Figure 2.

Figure 3 shows the survival of those with negative skeletal scintigraphy grouped on the basis of raised or normal serum PAP. There is no statistically significant difference between the survival of these groups having normal skeletal scintigraphy, irrespective of PAP. The survival of those with abnormal scans differs significantly from that of both other groups ($\chi^2 = 21.04$, $P < 0.001$, in the case of the difference between the survival curve for

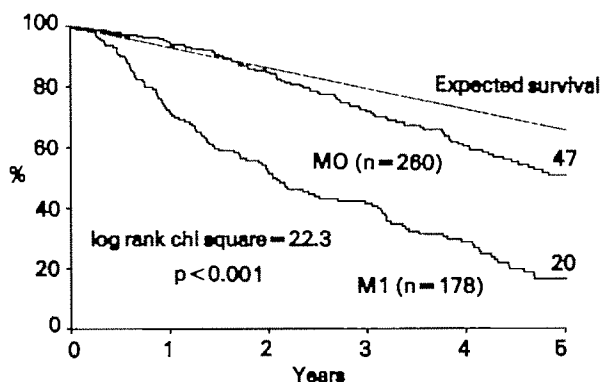


Fig. 1 Actuarial survival of all patients (deaths due to all causes) grouped on the basis of scintigraphic findings at diagnosis.

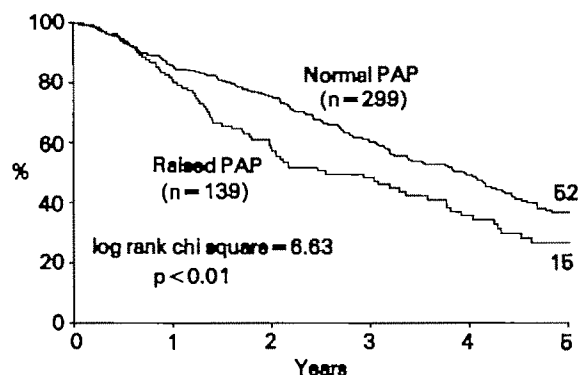


Fig. 2 Actuarial survival of all patients (deaths due to all causes) grouped on the basis of serum PAP at the time of diagnosis.

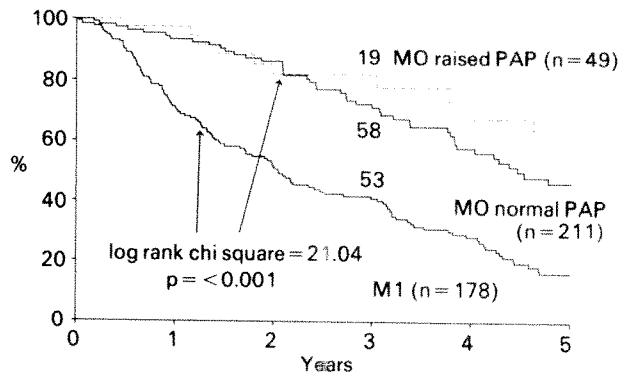


Fig. 3 Actuarial survival of patients with positive scans at diagnosis and of those with negative skeletal scintigraphy grouped on the basis of raised or normal serum PAP.

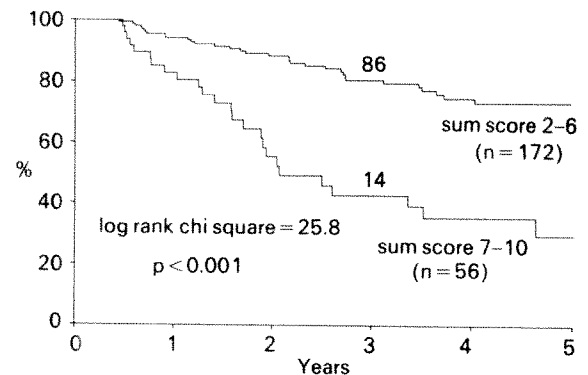


Fig. 5 Progression to skeletal metastases of 228 patients having normal scintigraphy at diagnosis (analysed by life table methods) grouped on the basis of Gleason sum score at diagnosis.

abnormal scans compared to that for normal scan and elevated PAP).

Progression to skeletal metastases of patients with normal scintigraphy at diagnosis was analysed by life table methods. In Figure 4 patients are grouped according to serum PAP at diagnosis, and in Figure 5 228 patients whose tumours were graded histologically by the Gleason grading system are grouped according to the Gleason sum score (26 patients had no Gleason score). Raised PAP level at diagnosis in this group is shown to indicate a significantly increased risk of developing skeletal metastases. Histological grade, however, is shown to be more powerful predictor of scan conversion.

Discussion

The recognition that serum prostatic acid phosphatase is an imperfect guide to tumour stage and to prognosis in prostatic cancer is not new (O'Dono-

ghue *et al.*, 1978; Merrick *et al.*, 1985). In certain circumstances, however, acid phosphatase has been reported as being unexpectedly sensitive. Bahnson and Catalona (1987) reported an increased risk of adverse pathological findings, in terms of extra-prostatic tumour extension, for patients with clinical localised prostate cancer whose acid phosphatase was no more than in the upper half of the "normal" range. It has been suggested that PSA correlates better with tumour stage than either PAP (Stamey *et al.*, 1987) or serum alkaline phosphatase (Emtage *et al.*, 1987). The prognostic value of prostate specific antigen has yet to be addressed, since the assay has only relatively recently become widely available.

This study confirms that serum PAP at the time of diagnosis is of some value as a prognostic indicator when considered alone. If, however, the bone scan is normal, an elevated PAP (as defined here) provides little additional prognostic information.

Elevated serum PAP, defined in the same manner as in this study, is used in the current MRC immediate versus deferred orchiectomy trial to define the presence of skeletal metastases when the bone scan is negative. Survival is one of the end points to be analysed in the MRC trial, and randomisation is stratified on the basis of presence or absence of skeletal metastases. The results of this study suggest that stratification on this basis may be inappropriate.

Merrick *et al.*, (1985), in an early report on part of the current series, showed that raised plasma alkaline phosphatase alone was at least as good as skeletal scintigraphy, and better than PAP, in predicting prognosis in prostate cancer. Although the definition of raised markers used in their report

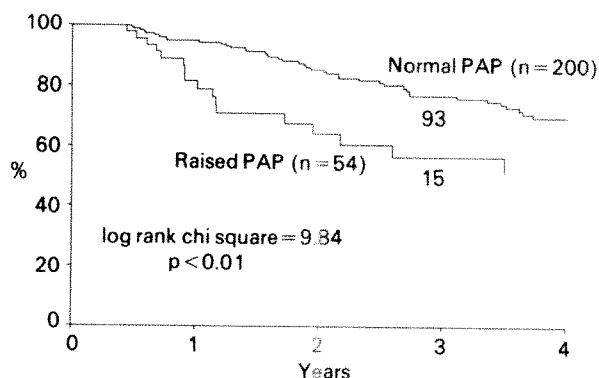


Fig. 4 Progression to skeletal metastases of 254 patients having normal scintigraphy at diagnosis (analysis of life table methods) grouped on the basis of PAP at diagnosis.

is not stated, reference to the original data shows that the authors used the upper limit of the normal range as the cut-off point for both acid phosphatase and alkaline phosphatase, so that direct comparison with this series is not possible. It is of interest to note, however, that 94% of patients in their series with both raised plasma alkaline phosphatase and raised PAP had skeletal metastases on bone scan. In the present series the equivalent figure is 89%, and only 5 patients had normal scans and yet had both tumour markers elevated (plasma alkaline phosphatase greater than twice the upper limit of the normal range). Survival analysis on this group is not valid and so the prognostic significance of this combination of factors cannot be assessed from these data.

Management of these patients was not uniform, and since management inevitably has some bearing on prognosis, the groups studied here may be thought incomparable. Although those with positive bone scans more often received immediate than deferred hormonal therapy, the management of patients in the 2 groups with normal scans was similar, except that 38 patients with normal PAP were treated with radical radiotherapy while only 1 patient with raised PAP received this treatment. Repeat analysis of survival, excluding those patients so managed, still shows no significant difference in survival of the 2 groups with normal scans, while the poorer survival of those with positive scans remains significantly different from that of both other groups. The results of this study cannot, therefore, be applied to prognosis of untreated prostate cancer but reflect more the course of the disease despite therapy and the results are interpreted in this context. In conclusion, this study suggests that raised serum prostatic acid phosphatase should not be considered to imply skeletal metastases if skeletal scintigraphy is normal. Impending skeletal metastases are better predicted by high histological tumour grade.

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Prostatic Specific Antigen Related to Clinical Status 1 to 14 Years after Radical Retropubic Prostatectomy

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Summary—Serum prostatic specific antigen (PSA by Tandem-R immunoassay) was measured in 190 patients after radical prostatectomy for prostate cancer. Serial measurements were made in all patients operated on in the past 3 years; 131 had undetectable levels and 59 had levels in the detectable range. Only 10% of the patients with undetectable PSA following surgery had seminal vesical involvement or positive lymph nodes. None of the patients with undetectable PSA have had clinical recurrence within the 41 months of mean follow-up. In 14 patients who had PSA serially measured since surgery, detectable levels were found within 6 months of operation and 7 of these patients had clinical progression within 2 years; 39 patients had detectable PSA after radical prostatectomy with no clinical evidence of recurrence. Biopsy of the anastomosis was performed in 11 patients with isolated detectable PSA after surgery and local recurrence was established in 4. PSA was detectable later in the follow-up of 45 patients operated on before the PSA assay became available but the date when PSA actually became detectable is not known. A relatively new method of estimating that date and constructing a corresponding Kaplan Meier curve is presented. PSA is an effective marker for monitoring patients after radical prostatectomy as it often detects early persistent disease in patients with detectable measurements 6 months post-operatively or recurrent disease in patients with later rising levels.

Prostatic specific antigen (PSA) is a glycoprotein first described by Wang *et al.* (1979). Its exact function is unknown, but it appears to have a role in semen coagulin liquefaction. PSA is produced only by prostatic tissue and anti-PSA antibodies do not usually react with other body proteins (Lilja, 1985). Therefore, after radical prostatectomy, levels of PSA should be undetectable in patients without prostatic tissue. PSA measurement 3 to 6 months after surgery is considered a good marker and undetectable levels indicate complete eradication of prostate cancer. Although some recent studies have addressed the issues of tumour volume, stage and grade in relation to PSA (Stamey *et al.*, 1989), evaluation of PSA in long-term follow-up after radical prostatectomy has not been widely published. This study examines the clinical status

related to PSA levels in 190 patients 1 to 14 years after radical prostatectomy.

Patients and Methods

Serum prostatic specific antigen levels were determined using the Tandem-R PSA immunoassay. The normal range by manufacturer's recommendation is 0 to 4 ng/ml and the value recommended for undetectable level is <0.2 ng/ml. To improve determination of the lower level of detection, our laboratory used pooled negative female sera as the zero control and the mean was used plus or minus 2 standard deviations. We designated <0.4 ng/ml as an undetectable level after complete removal of the prostate.

Post-operative follow-up PSA levels were available on 242 patients who had undergone radical retropubic prostatectomy for clinically localised

prostate cancer between 1977 and 1989; 47 patients who had received any kind of adjuvant treatment for locally extensive tumours were excluded (24 had adjuvant radiotherapy for tumours which had penetrated the capsule or involved the seminal vesicles and 23 had adjuvant hormones, radiotherapy or chemotherapy for lymph node involvement). Five patients who progressed before their PSA was measured were also excluded. The remaining 190 patients formed the basis for this retrospective study and follow-up PSA measurements were made.

All patients had negative pre-operative prostatic acid phosphatase levels. Clinical staging was determined by the modified Whitmore-Jewett system. Pre-operative PSA levels were available on 51 patients. In 128 cases the potency nerves were spared at least on one side. Pathological staging was determined by histological examination of the pelvic lymph nodes and by whole mount step sections of the prostate.

The patients' mean age was 65 years (range 46–80). Digital rectal examination, prostatic acid phosphatase measurement and bone scans were performed every 6 months following surgery. PSA has become part of the routine post-operative follow-up in the last 3 years and has been serially measured in all patients operated on within the last 4 years. Follow-up PSA has recently been obtained on all patients who had undergone surgery before then.

Results

Post-operative follow-up ranged from 3 to 162 months (mean 45); 49 patients have been followed up for 5 years or more and 10 have been followed for at least 10 years.

Pre-operative PSA and clinical and pathological staging

Post-operative pathological staging revealed that 99 patients had organ-confined tumours (Group 1), 56 had tumours penetrating into or through the capsule (Group 2), 18 had tumours involving the seminal vesicles (Group 3) and 17 had lymph node involvement (Group 4). The Gleason sum score was greater than 7 in 25 patients and less than 7 in 167 (Table 1). Pre-operative PSA values were measured in 51 patients with a median PSA level of 5.3 ng/ml. There was no difference in the median PSA levels between organ-confined disease (5.3 ng/ml) and capsular involvement (5.4 ng/ml) (Fig. 1). The 4 patients with seminal vesical invasion had a mean pre-operative PSA measurement of 2.8 ng/ml.

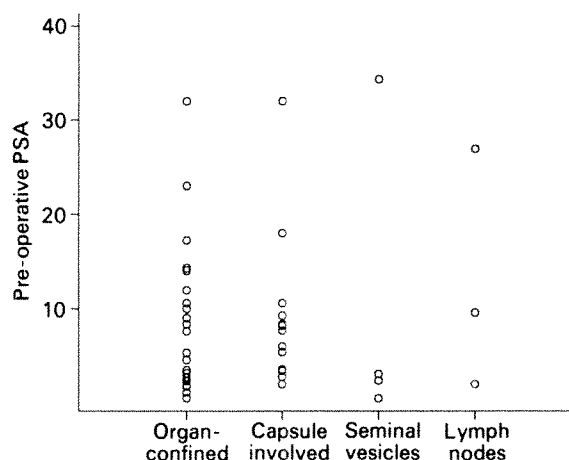


Fig. 1 Pre-operative PSA measurements in 51 patients. Relationship with pathological staging.

Table 1 Patient Characteristics of Local Tumour Extension

	<i>Organ-confined</i>	<i>Capsule involvement</i>	<i>Seminal vesicles</i>	<i>Lymph nodes</i>	<i>Total</i>
No.	99	56	18	17	190
Age (years)	65	65	66	64	65
Median pre-operative PSA value	5.3	5.4	2.8	9.6	5.3
	(n = 27)	(n = 17)	(n = 4)	(n = 3)	(n = 51)
% Gleason > 7	8	14	28	24	13
% Progressed	2	13	33	29	11
% Detectable PSA	16	36	67	65	31
Mean follow-up months	44	42	39	57	45

Time to disease progression

Twenty patients have had disease progression, with a mean time to progression of 37 months. Based on a Kaplan Meier curve, 17% progressed within the first 5 years. The time to progression depends on the post-operative level of tumour extension (Fig. 2). Since 45% of patients with positive lymph nodes also have seminal vesicle involvement, groups 3 and 4 have been combined in this figure. The 3-year estimated progression rates for the 3 groups are 1% for group 1, 16% for group 2 and 33% for groups 3 and 4 combined.

PSA after radical prostatectomy

Of the 190 patients with follow-up PSA measurements, 59 had detectable levels (31%). Of the 45 patients with repeated detectable assays, 36 were rising, 3 have remained stable and 6 have returned to undetectable levels. A total of 20 patients had clinical progression. Distant metastases were detected in 13 patients and local recurrences in 7. No patient with clinical recurrence had undetectable PSA at the time of progression. The number of patients progressed per year of follow-up in patients with detectable PSA was 0.08 (Table 2). Biopsy of the anastomosis between bladder and urethra was positive in 4/12 patients (30%) performed for "isolated" detectable PSA. All 4 patients had rising levels. Pathological staging showed invasion through the capsule in 3 patients and seminal vesicle invasion in 1. The mean Gleason was 6.2. Local recurrence was treated by radiotherapy.

A 6-month post-operative PSA value was available in 58/190 patients (Table 3), 14 of whom had

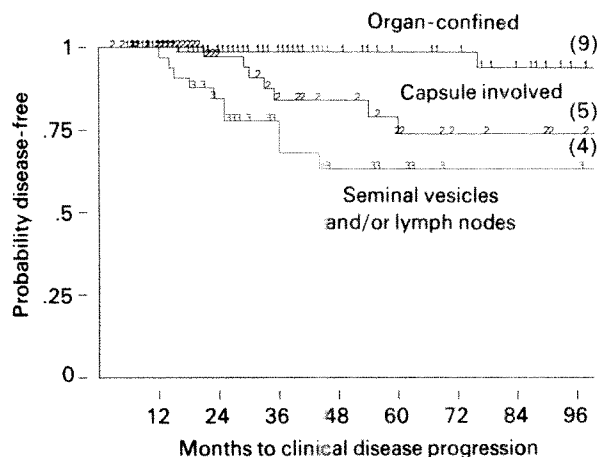


Fig. 2 Disease-free survival related to degree of local tumour extension. The small numbers along the curves represent ticks.

Table 2 PSA Status

	Undetectable	All detectable	Detectable at 3-6 months
No.	131	59	14
% Gleason > 7	8	24	43
Mean follow-up (months)	41	51	21
No. of progressions per year of follow-up	0	0.08	0.28
Tumour extension (%)			
Organ-confined	63	28	21
Capsule involvement	27	34	29
Seminal vesicles	5	20	29
Lymph nodes	5	18	21

detectable PSA when first measured (12 had rising levels). Seven of the 14 patients (50%) developed clinical progression within 30 months of surgery and 1 additional patient who became detectable 9 months after surgery also progressed at 29 months. Two of these patients had local recurrences and 5 developed bony metastases. Median follow-up was 21 months. The Gleason sum scores and the extent of local tumour (groups 1-4) are demonstrated in Table 3. The relationship between detectable PSA values and time is shown in 11 patients with several detectable measurements (Fig. 3). The curvature in these graphs suggests that the PSA values increase exponentially over time once they become positive. Figure 4 displays the Kaplan Meier curves where time to progression in patients with 6-month detectable PSA values is compared with time to progression in patients with undetectable 6-month PSA values. Within the first 3 years, 70% of patients with early positive PSA values are predicted to progress.

Table 3 Patients with Post-operative PSA (3-6 months)

	Undetectable PSA	Detectable PSA	Total
No.	44	14	58
% Gleason > 7	14	43	21
Age (years)	67	63	66
Mean follow-up (months)	18	22	19
Tumour involvement (%)			
Organ-confined	57	21	48
Capsule involvement	41	29	38
Seminal vesicles	2	29	9
Lymph nodes	0	21	5
No. progressed	1	6	7

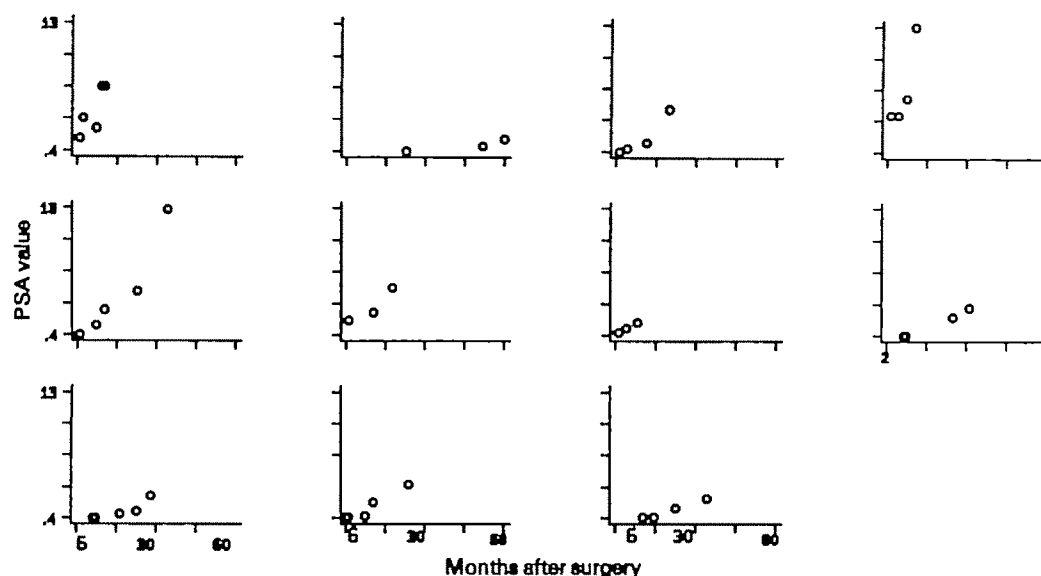


Fig. 3 Serial post-operative detectable PSA values in 11 patients with at least 4 detectable measurements. X-axis: time from surgery; Y-axis: PSA level.

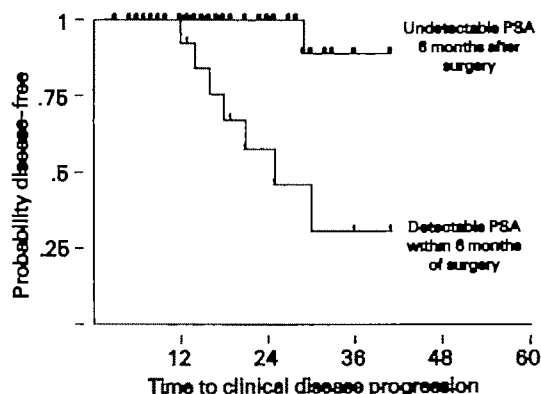


Fig. 4 Kaplan-Meier curve for time to clinical disease progression in 58 patients with PSA levels available 3 to 6 months after surgery. Time is measured from date of surgery.

Time from detectable PSA to disease progression

The interval between the first post-operative detectable PSA and clinical disease progression is unclear because many patients were operated on before PSA was available. In 132 patients PSA was not first measured until a mean of 52 months after surgery and 48 of these patients were already detectable at that time.

For all 59 patients with detectable PSA a Kaplan Meier curve was constructed for time from observed detectable PSA to clinical disease progression by considering the first time that a detectable PSA was

observed to be the time that the PSA was actually first detectable. This resulted in an estimate that 85% of the patients would progress within the first 3 years of being detectable.

Since we know that our estimate of 85% is too high, a better estimate can be obtained by trying to estimate (impute) when the patients actually first became detectable and then form the Kaplan Meier curve based on these imputed estimates. Based on the curvature in the graphs in Figure 3 it seems reasonable to assume that once the PSA value becomes detectable the PSA value over time will follow the pattern of an exponential curve (i.e. the log of the PSA value is linear over time). We calculated the exponential curves for the 11 patients in Figure 3 and found that the range of the 11 slopes was 0.02 to 0.13.

First we randomly chose a slope from the range 0.02 to 0.13 and then, using the observed detectable PSA value at the given time after surgery, we solved the linear equation for the time when the PSA value first reached the detectable level 0.4. In this way a patient with a higher PSA value will on average be expected to be detectable earlier than a patient with a lower PSA value. We performed this procedure for each patient where we did not know the actual time when 0.4 was reached and then calculated the Kaplan Meier curve for time to progression based on these estimated times. We repeated this procedure 4 times (called multiple imputation in the

statistical literature) and averaged the subsequent 4 Kaplan Meier curves in order to get an average estimated Kaplan Meier curve for the time from first becoming detectable to clinical progression (Fig. 5). This resulted in an estimate that 45% of patients would progress during the first 3 years after first reaching the 0.4 ng/ml detectable level. The estimate from this procedure is quite different from our earlier 85% estimate and illustrates how much of a possible bias exists by presuming that the time we first observed the PSA value to be detectable is the same as the time that the patient actually first became detectable.

Once the PSA becomes detectable the other prognostic factors, such as tumour extension and Gleason sum score, no longer provide any further information in terms of time to clinical disease progression. Using the imputed values for the time PSA was first detectable, we found that the time from detectable PSA to clinical progression was not significantly related to local tumour progression ($P=0.191$) and was not related to whether the Gleason sum score was greater than 7 ($P=0.614$).

Discussion

Pre-operative PSA values have been used to predict local tumour extension. Stamey *et al.* (1989), using the polyclonal PSA assay, reported good correlation between pre-operative PSA levels and tumour volume, capsule penetration and seminal vesicle

involvement. In general, PSA values have been shown to increase with advancing clinical and pathological stage (Osterling *et al.*, 1988; Hudson *et al.*, 1989). However, on an individual basis, pre-operative PSA was not sufficient to predict which patient would have organ-confined disease and which would have extracapsular tumour extension (Lange *et al.*, 1989). Our data show a poor predictive value for pre-operative PSA levels in terms of pathological stage and grade. Special attention has been focused on the undetectable level of PSA as it has become an important marker in evaluating post-radical prostatectomy patients. PSA is produced only by the prostate and has a half life of 2.2 ± 0.3 days (Stamey *et al.*, 1987). After complete removal of the prostate, therefore, PSA should come down to an undetectable level within 6 months of surgery.

The lower limit of detection in the R-Tandem PSA assay has shown interlaboratory variations. We designated ≤ 0.4 ng/ml as the post-operative undetectable level (Lange *et al.*, 1989).

Endocrine treatment is known to reduce the number of PSA-producing cells and adjuvant therapy for lymph node involvement may result in false negative post-operative (undetectable) levels. Post-operative PSA may also be unreliable in patients receiving adjuvant radiotherapy for locally invasive tumours. Patients with any kind of adjuvant post-operative treatment were therefore excluded from this study (Lange and Brawer, 1989).

Detectable and rising PSA 6 months post-operatively implies persistent prostate cancer after radical prostatectomy. These patients have a higher and earlier progression rate. The present study included 14 patients with detectable PSA 6 month post-operatively and 7 of them progressed clinically within 2 years. Figure 3 illustrates the post-operative PSA serially measured in 11 patients with detectable PSA after radical prostatectomy. All had at least 4 detectable PSA measurements after surgery and there is a clear curvature in the graphs; 44 patients had undetectable PSA at 6 months.

If PSA is undetectable at the 6-month measurement and becomes detectable at a later date, it may be an early representation of recurrent disease. Only 1 patient in our study had clinical progression at 2 years after having undetectable PSA at 6 months.

If detectable PSA is considered clinical progression, treatment of the recurrence is warranted. Some difficulty arises when type of treatment has to be selected. Radiotherapy would be effective in treatment of local, clinically still undetectable

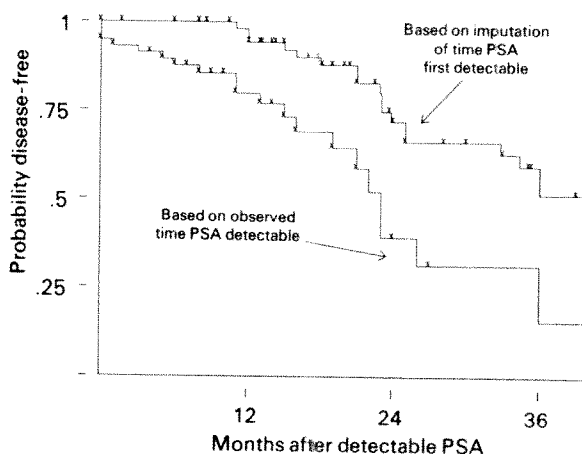


Fig. 5 Kaplan-Meier curve estimating time from detectable PSA to clinical progression. One curve is based on time measured between the date PSA was first observed to be detectable; the second (upper) curve measures the interval from the time PSA was estimated to be first detectable (using multiple imputation; see text) to clinical progression.

recurrence. If the detectable PSA, however, represents occult metastatic disease, hormonal treatment is recommended. Thus treatment of choice for patients with isolated detectable PSA following radical prostatectomy is not yet established.

A total of 132 patients had an initial PSA measurement 7 months to 13 years after surgery (mean 52 months). Overall, 131 patients had undetectable levels and 59 had PSA within the detectable range. Considering that date as the date of detectable PSA and measuring time to progression resulted in a short follow-up and early recurrences. Hudson *et al.* (1989) reported 70% recurrence within 3 to 5 years. In the present study, the mean time from date of detectable PSA to last follow-up was 14 months. Twenty patients have had clinical progression within the follow-up period. Biopsy of the anastomosis in patients with detectable and rising PSA levels revealed 36% with local recurrence. Lange and Brawer (1989) reported 42% with positive biopsies. These patients were treated by radiotherapy for local control of the tumour.

As we indicated earlier, all estimates of time from positive PSA to progression contain a bias unless the time when the patient first became positive is not known. Using a procedure that assumed an exponential relationship between time and PSA value, we estimated that about 45% of patients would actually progress within the first 3 years compared to an estimate of 85% if we used the time when the PSA value was first observed to be positive. The major point is not whether the exponential model is the best method of estimating the missing time when the PSA actually first became positive, but rather that by using reasonable methods of estimating the missing data we illustrate the bias involved in using the observed time of detectable PSA for estimating the time to progression. Our estimation procedure is based on actual patient data and introduces a certain amount of randomness to account for differences between individual patients.

The only way to guarantee a better estimate is to undertake a prospective follow-up of patients, measuring their PSA at least once a year until they become positive, and then to follow them up for 4 to 5 years or until they progress. Our earlier estimate of time to progression for the patients who were positive immediately after surgery cannot be used since they represent a population of patients in whom the disease was not eradicated at surgery. In addition, since some patients are beginning to be treated following detectable PSA levels, it will

probably be impossible to obtain better estimates in the future. This procedure of multiple imputation has been used recently in attempts to estimate the time from HIV exposure to clinical presentation of AIDS in patients (Taylor *et al.*, 1990).

It is concluded that a detectable level of PSA immediately after radical prostatectomy is a manifestation of residual prostate tissue. Rising levels imply persistent prostate cancer, though not all patients have demonstrated clinical recurrence. These patients should be studied for recurrence, since some who have a small recurrence in the area of anastomosis may still be cured by radiotherapy. Whether early therapy with the new hormonal agents is beneficial is not known.

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Study of the Seminal Vesicles in Acute Epididymitis

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Summary—Although it has been suggested that seminal vesiculitis is present in patients with epididymitis, it has not been proven. We performed rectal ultrasound assessment of the seminal vesicles in 18 consecutive patients with epididymitis. The seminal vesicle on the same side as the epididymitis was significantly enlarged in 75% of cases; 92% of these enlarged vesicles returned to normal size in 12 weeks.

A persistently enlarged seminal vesicle was associated with unresolved epididymitis, and further bacteriological studies in these cases demonstrated continued *Chlamydia* infection in some patients over 35 years of age.

Although seminal vesiculitis or prostatitis has been suggested to be present in cases of acute epididymitis this has never been proven (Handley, 1946; Wesson, 1959, 1963).

In the past, no cause could be found in the majority of cases of acute epididymitis and they were therefore labelled “idiopathic” (Ross and Maynard, 1957; Gartman, 1961; Mittenmeyer *et al.*, 1966; Furness *et al.*, 1971; Shapiro and Breschi, 1973). Recent studies have shown that *Chlamydia trachomatis* is a common cause of epididymitis in men under 35 years of age, and coliform infection is the major cause in older men (Berger *et al.*, 1978, 1979).

We were under the impression that the seminal vesicles often felt enlarged in patients with epididymitis. This study was therefore undertaken to determine:

- If the seminal vesicles were indeed enlarged in patients with acute epididymitis.
- The aetiology in these cases.
- The diagnostic yield of bacteriological investigations, including the Chlamydiazyme test in this group of patients, many of whom had already received antibiotic treatment.

Patients and Methods

Eighteen consecutive men with suspected acute epididymitis were seen between July 1986 and February 1987 (Table 1). All had unilateral pain and swelling of the epididymis; 9 patients were taking antibiotics prescribed by their family doctor prior to admission. Each patient was examined by the investigator. One underwent scrotal exploration to exclude torsion of the testis.

Microbiological studies

A swab (STD Sample, Collection and Transport Kit, Abbot Laboratories) was passed into the anterior urethra for a distance of 2 to 4 cm in each patient. This was subsequently tested for *Chlamydia*, using an immunoassay technique (Chlamydiazyme Diagnostic Kit, Abbot Laboratories). First void, mid-stream and post-prostatic massage specimens of urine for microscopic examination and aerobic culture on McKonkey's medium were taken and 3 early morning samples of urine were cultured for acid-fast bacilli.

Ultrasound scan

Transrectal ultrasound scan of the seminal vesicle was performed in all patients, using a Bruel and Kjaer transrectal scanner, with the 4 MHz/5.5 MHz transducer set at a focal length of 2 to 7 cm. The echo pattern and the maximum area and

perimeter of both seminal vesicles were measured in the transverse plane. A photographic record was kept. (Volumetric measurement of the seminal vesicles is difficult but it is relatively easy to record the above measurements). The bacteriological examination and scans were performed on admission and repeated 8 to 12 weeks later. Seminal vesicle scans were also performed in 18 age-matched controls to define normal measurements and appearances.

Results

Of the 18 patients studied, 10 were under 35 years of age (Table 1); the right side was affected in 10 and the left side in 8.

Fifteen patients were referred in the acute stage, 4 h to 5 days after onset. Three patients were referred 1 to 8 weeks later. Only 5 patients had urinary symptoms. Four patients had a history of previous epididymitis (3 on the same side); 6 patients had been given Septrin and 3 amoxycillin prior to admission. Nine patients had had no sexual intercourse in the 6 weeks prior to the onset of symptoms. Of the 5 patients with a history of recent sexual intercourse, this had occurred with a new partner in 3 cases. No data were available on 4 patients.

Table 1 Age of Patients

	< 35 years	> 35 years
No. of patients	10	8
Age range	19-34	37-83
Mean age	26.7	52

Bacteriology

Six of the 10 patients in the younger age group had pyuria (>10/HPF) in at least 1 sample of urine. Urine culture was positive for *Escherichia coli* in 1 patient and sterile in the rest. Urethral swabs were positive in 3 patients for *Chlamydia*. In 3 patients, although the urine contained pus cells, it was sterile on culture and the urethral swab was also negative for *Chlamydia*. On the other hand, 1 patient with no pus cells in the urine was positive for *Chlamydia*. Although 5 patients in this group were on antibiotics prior to admission, *Escherichia coli* was cultured from the urine of 1 patient. Another patient, who had been on amoxycillin for 2 weeks, had a positive urethral swab for *Chlamydia*.

All 8 patients in the older age group had pus cells in their urine. One patient's urethral swab was

positive for *Chlamydia*. Urine culture in 4 patients was positive for bacteria, with *Escherichia coli* being the organism in 3 and *Klebsiella* and *Enterobacter* in 1. Although 4 patients were on antibiotics prior to admission, urine culture was positive for *Escherichia coli* in 1 patient and the urethral swab was positive for *Chlamydia* in another.

Transrectal ultrasound

In a control group of 18 normal men (Table 2), the mean area of the right seminal vesicle determined ultrasonically was 2.1 sq cm (range 1.0-3.8) and that of the left was 2.3 sq cm (range 0.9-3.2). Both vesicles were of equal size in 8 cases. One vesicle was slightly larger than the other in 10 cases.

Although the seminal vesicles may vary in size when measured at different times, they are usually of equal size. In none of the control group was the difference in size between the 2 seminal vesicles greater than 0.3 sq cm.

A seminal vesicle was considered to be enlarged in the acute epididymitis group if its area was 0.3 sq cm larger than the opposite side.

Table 2 Size (area and perimeter) of Normal Seminal Vesicles in 18 Age-matched Controls

	Right seminal vesicle		Left seminal vesicle	
	Area (cm ²)	Perimeter (cm)	Area (cm ²)	Perimeter (cm)
Range	1.0-3.8	4.5-11.4	0.9-3.2	4.1-11.6
Mean	2.1	6.9	2.3	7.6

Acute stage

Of the 10 patients with acute right epididymitis, the seminal vesicle on the same side was enlarged in 8 cases ($P < 0.001$). In 1 patient there was no enlargement and the opposite seminal vesicle was enlarged in 1 (Table 3).

It was possible to perform a scan in only 7 of the 8 patients with acute left epididymitis. The left seminal vesicle was enlarged in 5 of these ($P < 0.001$) and in 2 cases there was no enlargement (Table 4).

A comparison of the "normal" side seminal vesicle during the acute stage and subsequently showed an initial mean enlargement 2.27:1.97 but this was not statistically significant ($P = 0.119$).

Follow-up

The scan was repeated 8 to 12 weeks after the acute attack in 17 cases (Tables 5 and 6). Five seminal

Table 3 Right Epididymitis—Size of Right and Left Seminal Vesicles on Admission

No.	Right seminal vesicle		Left seminal vesicle		Comment
	Area (cm ²)	Perimeter (cm)	Area (cm ²)	Perimeter (cm)	
1	4.1	9.9	2.8	7.8	Rt. enlarged
2	4.0	13.0	1.3	7.3	Rt. enlarged
3	5.2	12.2	3.7	10.7	Rt. enlarged
4	3.2	8.4	2.0	7.6	Rt. enlarged
5	3.0	8.2	2.1	7.8	Rt. enlarged
6	1.0	5.1	1.3	6.6	No enlargement
7	2.9	7.6	3.4	8.2	Lt. enlarged
8	5.0	11.0	3.5	6.3	Rt. enlarged
9	4.4	10.0	1.5	6.5	Rt. enlarged
10	4.9	13.7	3.7	11.5	Rt. enlarged
Mean	3.8	9.9	2.5	8.0	

Table 4 Left Epididymitis—Size of Left and Right Seminal Vesicles on Admission

No.	Left seminal vesicle		Right seminal vesicle		Comment
	Area (cm ²)	Perimeter (cm)	Area (cm ²)	Perimeter (cm)	
1	4.7	9.7	2.4	6.7	Lt. enlarged
2	1.3	7.1	1.2	5.9	No enlargement
3	2.6	7.4	2.4	7.4	No enlargement
4	2.2	7.2	1.0	5.0	Lt. enlarged
5	4.0	9.6 (echo+)	3.2	8.8 (thick wall)	Lt. enlarged
6	3.6	8.9	1.8	4.6	Lt. enlarged
7	3.9	8.3 (echo+)	2.7	7.5	Lt. enlarged
8	—	—	—	—	Not done
Mean	3.2	8.3	2.1	6.6	

Table 5 Right Epididymitis—Repeat Scan 8–12 Weeks after Acute Attack to Assess Size of Seminal Vesicles

No.	Right seminal vesicle		Left seminal vesicle		Comment on right seminal vesicle
	Area (cm ²)	Perimeter (cm)	Area (cm ²)	Perimeter (cm)	
1	1.6	6.4	2.5	7.9	Shrunk
2	1.0	4.5	1.8	7.1	Shrunk
3	3.8	11.5	3.0	10.1	Still enlarged
4	1.8	5.4	1.6	5.2	Equal
5	1.0	6.4	1.4	6.9	Shrunk
6	1.6	6.2	1.7	5.6	Equal
7	1.8	6.3	1.8	6.7	Equal
8	1.0	5.1	1.3	6.6	Shrunk
9	1.8	6.8	1.7	6.7	Equal
10	3.0	10.2	3.2	10.6	Equal
Mean	1.84	6.88	2.0	7.34	

Table 6 Left Epididymitis—Repeat Scan 8–12 Weeks after Acute Attack to Assess Size of Seminal Vesicles

No.	Left seminal vesicle		Right seminal vesicle		Comment of left seminal vesicle
	Area (cm ²)	Perimeter (cm)	Area (cm ²)	Perimeter (cm)	
1	1.4	7.6	2.2	7.6	Shrunk
2	—	—	—	—	Not done
3	3.2	9.6	2.6	7.8	Late enlargement
4	1.6	6.3	1.4	6.0	Equal
5	2.5	8.5	2.4	8.7	Equal
6	1.5	6.4	1.5	6.1	Equal
7	0.9	4.1	1.0	4.2	Equal
8	1.6	6.8	1.8	6.9	Equal
Mean	1.81	7.04	1.84	6.7	

vesicles that had been enlarged were now smaller than the opposite normal vesicle (Fig. 1); this difference failed to reach significance (mean 1.87 compared to 2.27 normal size, $P=0.079$). Seven previously swollen seminal vesicles were now the same size as the opposite normal vesicle (Fig. 2) and 1 remained enlarged (Fig. 3). Those that were previously unaffected remained unchanged except for 1 which showed late enlargement at 8 weeks (Fig. 4).

Discussion

Reflux of sterile urine from a full bladder during stress such as coughing or sneezing (Graves and

Engel, 1950) or straining at stool (Abeshouse and Lerman, 1950) have been suggested as causes for epididymitis. Handley (1946) and Wesson (1959, 1963) disagreed with this concept and thought that infection from prostatitis or seminal vesiculitis was the inciting factor in almost all cases. Until recently it was not possible to image the seminal vesicle by a non-invasive technique, so that this theory remained unproven. The availability of transrectal ultrasound scanning has now made the study of seminal vesicles possible by a relatively non-invasive technique.

This study has shown that the ipsilateral seminal vesicle was significantly larger than its mate in 72 to 80% of cases of unilateral acute epididymitis.

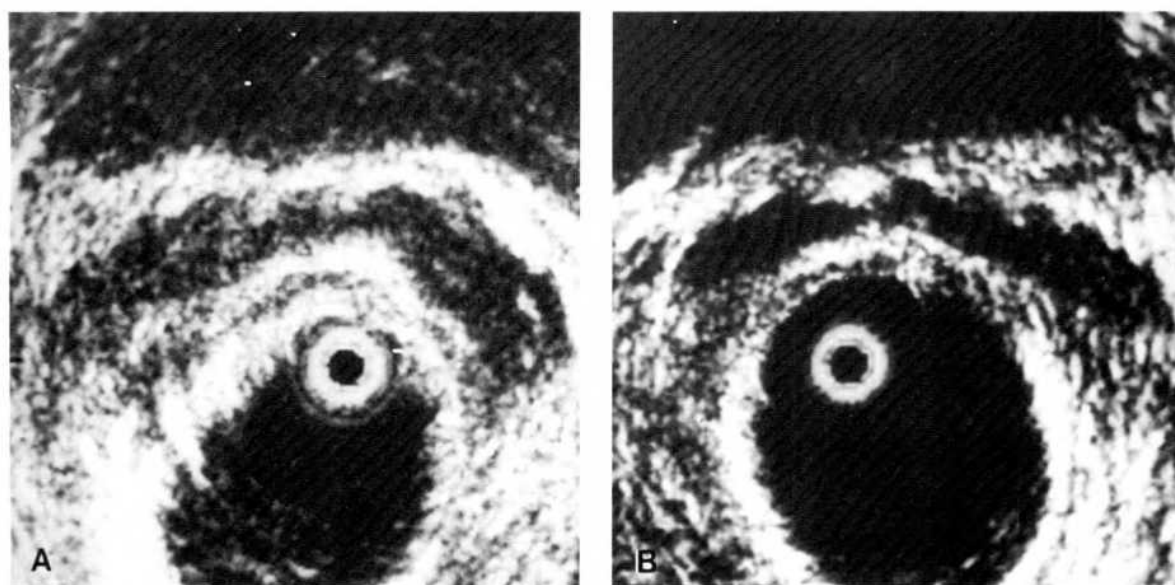


Fig. 1 (A) Ultrasound scan of seminal vesicles in acute right epididymitis. The right seminal vesicle is enlarged with echogenic contents. (B) Repeat scan 8 weeks later shows that the right seminal vesicle has shrunk and is smaller than the opposite side.

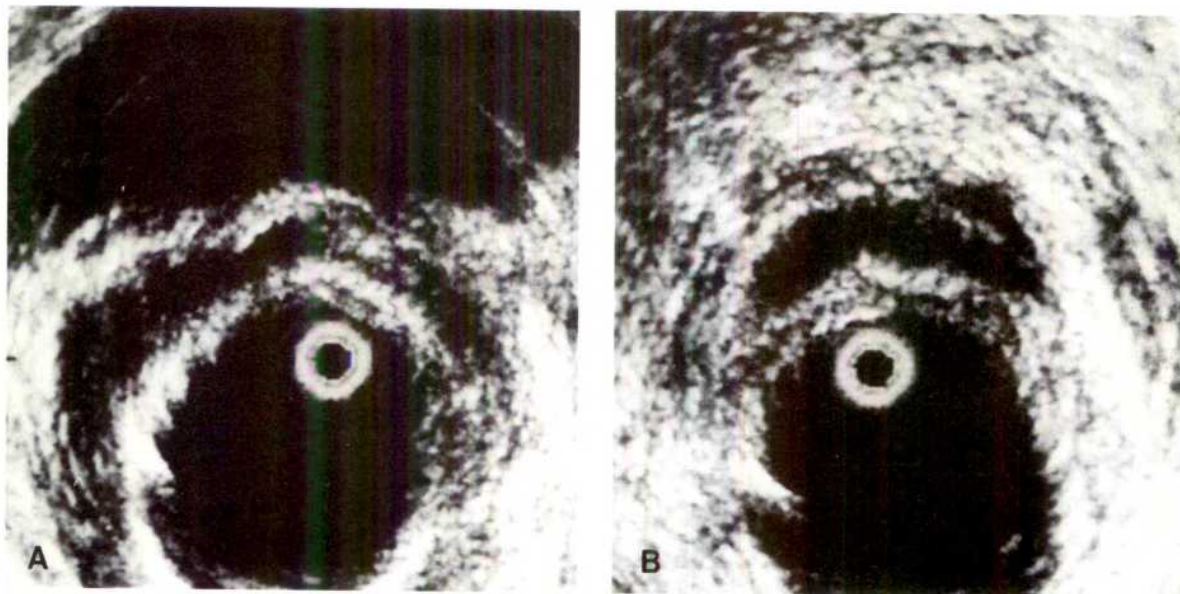


Fig. 2 (A) Ultrasound scan of seminal vesicles in acute right epididymitis. The right seminal vesicle is enlarged. (B) Repeat scan 4 weeks later shows that the right seminal vesicle enlargement has now resolved and both vesicles are the same size.

There was no significant difference in the gland on the uninvolved side either before or after treatment ($P=0.119$); 54% of these enlarged vesicles returned to normal size in 8 to 12 weeks and a further 38% became smaller than the opposite vesicle, although this failed to reach statistical significance. We

postulate that this swelling is due to an inflammatory condition similar to that in the ipsilateral epididymis and that this condition is present early in the onset of epididymitis. It is noteworthy that the opposite seminal vesicle is rarely involved.

Resolution usually occurs within 8 to 12 weeks. The 1 patient with epididymitis that persisted for 10 weeks also had a persistently enlarged seminal vesicle of an unusual configuration, it being enlarged in the distal segment. Whether seminal vesiculitis is the cause or the result of epididymitis is not known because it has not been possible to scan the seminal vesicle prior to epididymitis. One patient had an initially normal seminal vesicle that enlarged 8 weeks later and this suggests that the relationship between epididymal and seminal vesicle inflammation may not be quite as simple as has been earlier suggested. This is a matter for further investigation.

Berger *et al.* (1978, 1979) showed that *Chlamydia trachomatis* was the causative organism in 50% of cases of acute epididymitis in men under 35 years of age, whereas coliforms were the cause in 75% of patients over 35 years of age. In their study there was a high proportion of patients referred from venereal disease clinics and student health clinics and none of the patients had received antibiotic treatment. These factors probably account for the high incidence of *Chlamydia trachomatis* infection in their series.

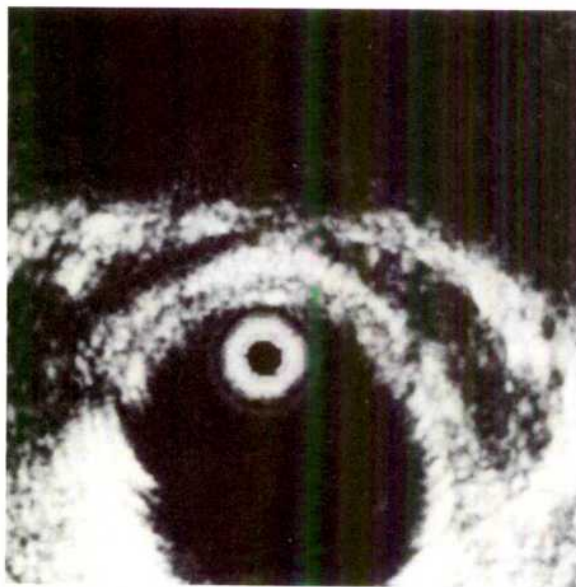


Fig. 3 Persistent right seminal vesicle enlargement 10 weeks after acute right epididymitis. Note that the cystic dilatation is confined to a segment.

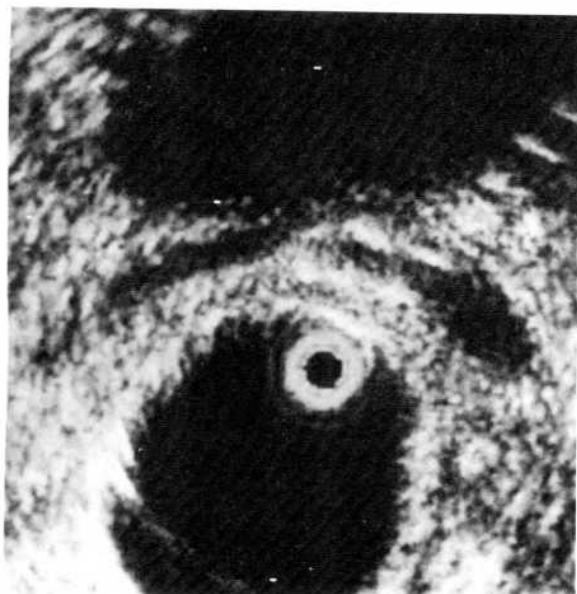


Fig. 4 Late enlargement of left seminal vesicle 8 weeks after acute epididymitis.

The patients in this study were referred from the community by their family doctors and 50% were already taking antibiotics prior to being seen by us. This probably accounts for the lower incidence of *Chlamydia trachomatis* and *Escherichia coli* epididymitis.

This difference may also be partly explained by the more detailed and exhaustive bacteriological and serological investigations undertaken by Berger *et al.* (1978, 1979). Although the actual incidence of both *Chlamydia trachomatis* and coliform infection was lower in this study, the pattern parallels the finding of Berger *et al.* We confirm that *Chlamydia trachomatis* is the commonest cause of acute unilateral epididymitis in men under 35 years of age in the general community, while *Escherichia coli* is the commonest organism in men over 35 years of age.

The ipsilateral seminal vesicle is almost always enlarged in unilateral acute epididymitis. Whether this is cause or effect is difficult to prove. The enlargement usually resolves within 3 months and in some cases the seminal vesicle appears smaller than the contralateral side. Persistent epididymal symptoms are associated with persistent enlarge-

ment of the seminal vesicle. Under these circumstances further swabs should be taken for *Chlamydia* and the patient and his sexual partner given a further course of antibiotics. *Chlamydia trachomatis* (in under 35-year-olds) and coliforms (in over 35-year-olds) are the commonest causes of acute epididymitis in an unselected population from the community. Since such patients are usually seen by the family doctors, who prescribe antibiotics after minimal or no bacteriological investigations, it is recommended that tetracycline or erythromycin be given to patients with epididymitis under 35 years of age. Ideally, a mid-stream specimen of urine for aerobic culture and urethral swab for Chlamydia-azyme test should precede the treatment.

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Urological Aspects of Behcet's Disease

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Summary—Behcet's disease, affecting mostly young males in the Mediterranean countries and Japan, is a multi-system disease with urological manifestations. In this prospective study of 100 consecutive patients with newly diagnosed Behcet's disease, we found that 89% of the males had experienced scrotal ulceration and 6% had epididymitis. We also observed sterile urethritis in 3%. Other urological abnormalities appeared to be coincidental findings.

Behcet's disease, first described by Turkish dermatologist Hulusi Behcet (1937), is more common in Mediterranean countries, the Middle East and Japan. Clinical manifestations include recurrent aphthous ulcers of the oral mucosa, skin lesions, genital ulceration, ocular inflammatory lesions, arthritis, epididymitis, intestinal ulcers, vascular lesions, neuropsychiatric symptoms and positive pathergy test (Nussenblatt and Palestine, 1989; International Study Group for Behcet's disease, 1990).

We have made a prospective study of 100 patients with Behcet's disease in order to detect urological abnormalities.

Patients and Methods

Between May 1988 and May 1990, 100 new patients with clinically diagnosed Behcet's disease were seen. The diagnosis was based on the presence of oral ulceration and any 2 of the following: genital ulceration, typical eye lesions, skin lesions or positive pathergy test as described by the International Study Group for Behcet's Disease (1990). Following diagnosis, the patients were interviewed by a urologist and asked if they had any urological complaints. A full physical examination, urine analysis and intravenous urography (IVU) were performed in all cases. The series comprised 70

males and 30 females, their ages ranging between 16 and 60 years (mean 30).

Results

In 78% of the patients no urological complaints were registered. Sixteen patients complained of frequency and nocturia and 2 had passed stones *per urethram*; 1 of these had had 2 previous operations for renal stones. Two patients had a urethral discharge and 2 others (aged 54 and 60) complained of minimal obstructive symptoms. Physical examination revealed active scrotal ulceration in 8 men and genital ulceration in 2 women. There were signs of scars from previous attacks of genital lesions in another 54 men and 24 women. In 4 men the epididymes were hard and nodular, suggesting previous episodes of epididymitis. A white male patient, aged 60, had absent testes and a scrotal incision scar; he stated that he had had a testicular abscess treated by bilateral orchiectomy 10 years previously. Another patient had bilateral flank incision scars following earlier stone removal. Two patients had a urethral discharge but direct microscopy was negative for micro-organisms and cultures were sterile. Urine analysis revealed pyuria in 3 patients and calcium oxalate crystals in 2.

IVU was normal in 93% of the patients. Two had signs suggestive of urogenital tuberculosis; this was later confirmed by direct microscopy and urine culture and antituberculous treatment was initiated. A further 2 patients had pelviureteric junction

(PUJ) obstruction which was corrected surgically. IVU revealed scarred kidneys with caliceal dilatation in 2 patients. Investigations for tuberculosis were negative and these were accepted as previous attacks of pyelonephritis. One patient had a ureteric stone which he passed spontaneously. Another patient with neurological signs of Behcet's disease had an acontractile detrusor with normal sphincteric mechanisms but he managed well with suprapubic compression.

Discussion

The aetiology of Behcet's disease remains unknown. Patients may present with signs and symptoms in various systems of the body but initial presentation with urological symptoms is not uncommon. In a survey of 2031 patients in Japan, genital lesions were present in 76% of the men and 83.8% of the women (Mishima *et al.*, 1979). In the male, genital lesions usually comprise painful skin ulcers in the scrotum or penis which may be deep and lead to scarring. Dressings, general hygiene and analgesics are the appropriate treatment.

Epididymitis, probably caused by vasculitis, has also been observed and needs no specific treatment other than analgesics. We found that 89% of our

patients had experienced scrotal ulceration and 6% had epididymitis.

In 3% of the males we found sterile urethritis with discharge. Urinary tuberculosis and PUJ obstruction in 2% of the patients appeared to be coincidental findings.

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Treatment of Organic Impotence

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Summary—A review of 86 patients referred to a urological clinic with impotence showed that in 58% the causation was predominantly psychogenic. These patients were managed with psychosexual counselling. The various treatment options were discussed with those patients with organic impotence and 14 underwent the implantation of a penile prosthesis.

A review of 130 patients who received penile prostheses in the period 1983 to 1987 was carried out to compare the complications and results obtained with the various types of prosthesis. The overall satisfaction rate was 81%; dissatisfaction usually arose as a result of complications of surgery. These were highest in patients with diabetes and priapism. The complications were also related to the type of prosthesis used.

The past decade has seen great interest in the treatment of patients with erectile dysfunction and it is now realised that many patients have an organic basis to their problem. The development of psychosexual counselling, the application of techniques such as the injection of vasoactive agents (Virag, 1982; Brindley, 1983), the use of external devices to assist erection and implantable penile prostheses, all need to be considered in the management of men with erectile impotence. During the past 3 years many new prostheses have become available but there are few reports of the results obtained by a single centre using the different types. In this study we review our experience of these newer prostheses.

Patients and Methods

In an attempt to determine the proportion of impotent men undergoing prosthetic surgery, the spectrum of patients referred for management of their impotence was ascertained by a review of 86 consecutive men referred with impotence for outpatient evaluation between December 1986 and February 1987. All patients were assessed on the basis of their history, examination, response to intracorporeal papaverine (Strachan and Pryor,

1987), nocturnal penile tumescence testing or dynamic cavernosography (Wespes and Schulman, 1981) as was appropriate.

Patients with predominantly psychological impotence, even if associated with some degree of erectile impairment, usually vasculogenic in origin, were referred for psychosexual counselling. These patients, together with men whose weak erection was insufficient to permit vaginal penetration, were offered the use of an erection aid. The Correctaid resembles a relatively thick walled condom from which the air may be aspirated between the sheath and the penis, thereby inducing an erection. The Correctaid stays fitted to the penis during intercourse. The Erecaid induces an erection in the same way but maintains the erection by using a plastic band to constrict the base of the penis.

New types of prosthesis have become available during recent years and in an attempt to assess these we have reviewed our experience with prostheses implanted in the period 1983 to 1987. The 130 men usually underwent operation for organic impotence and the aetiology is shown in Table 1.

The type of prosthesis, incision and the complications were ascertained in the 115 men who had undergone operation at least 6 months previously. The result was considered to be satisfactory when the patient was able to have satisfactory intercourse

Table 1 Aetiology of Impotence

	No.	(%)
Diabetes mellitus	33	(25)
Pelvic surgery	11	(8.5)
Fractured pelvis	10	(8)
Neurogenic	9	(7)
Vascular	19	(14)
Peyronie's disease	23	(18)
Priapism	10	(8)
Psychogenic	4	(3)
Miscellaneous	11	(8.5)
Total	130	(100)

regardless of whether or not there had been a previous complication. Complications were examined in detail and with particular reference to post-operative pain, infection, erosion and the subsequent need to remove the prosthesis. These complications were correlated with the type of prosthesis and the aetiology of the impotence.

Results

Of the 86 patients who were referred to St Peter's Hospital over a 3-month period for the treatment of impotence, 50 (58%) had predominantly psychogenic impotence. Psychogenic impotence was diagnosed on the basis of the history, physical examination and a normal response to intracorporeal papaverine in the absence of a neurological deficit or with normal sleeping erections; 12 regained potency with no more than simple advice and counselling in the clinic and 38 were referred for psychosexual counselling; some patients failed to attend for this. Papaverine was not used as an initial treatment option for men with psychogenic impotence but was useful in conjunction with psychosexual counselling.

The remaining 36 patients (42%) had predominantly organic impotence. One had a soft glans and intercourse was still possible. Three men had venous leaks demonstrated by dynamic cavernosography and the remaining 32 men were candidates for the implantation of a penile prosthesis. Three of these patients had neurogenic impotence and elected to be managed by self-injection with papaverine; 2 of these patients suffered from advanced multiple sclerosis and the third, who had developed major problems following an anterior resection for a colonic carcinoma and had spent 3 months in an intensive care unit, declined any further surgery. The Correctaid and the Erecaid rely on suction pressure to initiate and maintain (Correctaid only)

the erection. Few people wished to try these techniques and none of the 7 patients who tried the Correctaid found it satisfactory.

Operation was declined by 15 men and a prosthesis was implanted into 14 (16%) of the 86 referrals. The type of prosthesis used and patient satisfaction with the outcome are shown in Table 2. A satisfactory outcome was obtained in 93 (81%) of the 115 patients evaluated and in general terms the outcome was unsatisfactory in those patients with post-operative complications, particularly when the prosthesis had to be removed. Complications related to the indications for surgery are shown in Table 3.

A complication-free post-operative course occurred in 67% of patients. Complications were most common in patients with diabetes (43%) or in those who had previously had a priapism (56%). It was least common in patients who were implanted because of previous pelvic surgery or injury. There was little difference in the incidence of troublesome post-operative pain in the various categories, but diabetics and patients with previous priapism were more prone to infection and this led to early loss of the prosthesis by either erosion or explantation.

Table 4 shows the incidence of complications related to the type of prosthesis implanted. The high incidence of complications in men receiving the Hydroflex prosthesis is immediately apparent, with only 18% having no post-operative complications at all. Post-operative pain (64%) and infection (36%) did not always lead to loss of the prosthesis (27%) but were sufficiently troublesome to account for the overall dissatisfaction rate of 45% with this prosthesis. Those patients with a successful Hydroflex prosthesis were very pleased with the results

Table 2 Type of Prosthesis Implanted and Patient Satisfaction

Type of prosthesis	No. implanted	Available for follow-up	Satisfactory result
Small-Carrion	63	56	49 (88%)
Subrini	2	1	1
Finney	5	4	4
Jonas	8	8	6
AMS 600	19	15	10 (75%)
Mentor Malleable	13	12	11 (92%)
Hydroflex	12	11	6 (55%)
Flexiflate	2	2	1
AMS 700	5	5	4
Mentor Inflatable	1	1	1
Total	130	115 (100%)	93 (81%)

Table 3 Complications of Penile Prosthetic Surgery related to Aetiology of Impotence

<i>Aetiology</i>	<i>No.</i>	<i>No complications (%)</i>	<i>Troublesome post-operative pain (%)</i>	<i>Infection (%)</i>	<i>Removal or extrusion of prosthesis (%)</i>
Diabetes	30	17 (57)	7 (23)	6 (20)	9 (30)
Priapism	9	4 (44)	2 (22)	2 (22)	3 (33)
Peyronie's disease	20	14 (70)	4 (29)	0	4 (20)
Vasculogenic	17	12 (71)	2 (12)	1 (6)	3 (18)
Pelvic surgery/fracture	18	16 (89)	2 (11)	0	1 (6)
Neurogenic	21	14 (67)	4 (19)	2 (10)	1 (5)
Total	115	77 (67)	21 (18)	11 (10)	21 (18)

and 1 such patient insisted on demonstrating the erectile and flaccidity capacity of the prosthesis to an audience of surgeons.

The AMS 600 prosthesis was complicated by a high incidence of troublesome post-operative pain (40%) and subsequent loss of prosthesis by erosion (3) or explantation (4), even though the incidence of infection was low. The high incidence of unsatisfactory results with the AMS 600 and Hydroflex prostheses was not related to a disproportionate number of patients implanted because of diabetes or following priapism (Table 5).

Discussion

It is of interest that the majority of patients referred to a urological clinic with impotence have predominantly psychogenic impotence, even though one suspects a bias in referral pattern towards patients with organic impotence. Many of the men (29%) were sufficiently reassured by the discussion at their out-patient visits (usually 2) not to require any further treatment. The remainder were referred for specialist psychosexual counselling.

Intracorporeal papaverine has been useful in the initial assessment of these patients but its therapeutic role remains uncertain. It is our practice to limit

its use to men with other problems—paraplegia, diabetes or multiple sclerosis—or to recommend its use in association with psychosexual counselling. Experience with the erection devices was disappointing; few patients elected to try the device and those who did found it unsatisfactory. It is thought that the Erecaid device might have been more satisfactory, as the erection is maintained with a plastic ring around the base of the penis and does not require the wearing of a relatively thick walled condom. This has not proved to be the case in our patients. The devices may have been unsatisfactory because of poor arterial flow.

Penile prostheses have a recognised role in the management of impotence. It is not surprising that there was a higher complication rate in diabetics and in patients following priapism, where dilatation of the corpora cavernosa can be difficult and result in perforation of the corpus and urethra. In these circumstances it is best to abandon the side with the perforation but implant into the intact corpus.

The overall loss of prosthesis was high (21, 18%), particularly as experience had been gained in 120 operations prior to the present series. However, diabetes and priapism accounted for the loss of 12 prostheses (57%) and a further 7 (33%) occurred in patients where the operation was carried out for

Table 4 Complications of Surgery in Relation to Prosthesis Implanted

<i>Prosthesis</i>	<i>No.</i>	<i>No complications (%)</i>	<i>Troublesome post-operative pain (%)</i>	<i>Infection (%)</i>	<i>Removal or extrusion of prosthesis (%)</i>
Small-Carrion	56	47 (84)	5 (9)	4 (7)	4 (7)
AMS 600	15	8 (8)	6 (40)	1 (7)	7 (47)
Mentor Malleable	12	10 (10)	1 (8)	0	1 (8)
Hydroflex	11	2 (2)	7 (64)	4 (36)	3 (27)
Others	21	10 (10)	2 (10)	2 (10)	6 (29)
Total	115	77 (67)	21 (18)	11 (10)	21 (18)

Table 5 Aetiology related to Type of Prosthesis

	<i>Small-Carrion</i> (%)	<i>AMS 600</i> (%)	<i>Mentor</i> <i>Malleable</i> (%)	<i>Hydroflex</i> (%)	<i>Others</i> (%)	<i>All types</i> (%)
Diabetes	12 (21)	3 (20)	5 (42)	3 (27)	7 (33)	30 (36)
Priapism	5 (9)	2 (13)	1 (8)	1 (9)	0	9 (8)
Other	39 (70)	10 (67)	6 (50)	7 (64)	14 (67)	76 (66)
Total	56	15	12	11	21	115

impaired blood supply or Peyronie's disease. The loss of prosthesis in patients where the operation was not associated with vasculogenic causes for impotence or diabetes was low, with only 2 prostheses being removed in the 45 patients operated upon in these categories.

There was a surprising difference in the complication rate with the different types of prosthesis, particularly as the Small-Carrion prosthesis was implanted in the earlier years. The poor results with the AMS 600 and Hydroflex require explanation, particularly as there was no bias in the type of patient undergoing operation. It is possible that the high incidence of complications with the Hydroflex may have been due to excessive tissue handling at the time of operation. This occurred partly from the desire to demonstrate that the inflation/deflation mechanism was working correctly and partly because the variation in stiffness at the time of surgery is often unimpressive. The true variation in erection/flaccidity is only apparent after 2 to 3 months. In view of this it is advisable to check the mechanism before implantation and minimise squeezing the tissues during operation. The high incidence of post-operative pain and erosion with the AMS 600 was also surprising and may stem from the newer design, which has made the prosthesis more rigid than earlier models. The manufacturers have subsequently modified the prosthesis in order to reduce its stiffness and this may reduce the complication rate.

The choice of penile prosthesis depends on many factors and satisfactory results can be obtained with each type. The more simple prostheses have a clear cost advantage and are satisfactory in most patients. Complaints about difficulties of dressing were rare. The self-contained inflatable prostheses (Flexiflate and Hydroflex) appeal greatly to both patient and surgeon. The inflation/deflation of these devices is better on the bench than in the

penis, although some improvement does occur after 2 to 3 months. These prostheses are undergoing modification and may yet prove to be satisfactory in the long run; certainly there have been some spectacular results with them. The multi-part inflatable prostheses have undergone many modifications and are now reliable. They are the choice for those who require complete flaccidity of the penis or for those who want the best of everything regardless of personal or insurance costs, or those in whom there are major problems in bladder function.

In conclusion, the choice of prosthesis depends on the patient's wishes, medical condition, costs and the quality of service provided by the prosthesis distributors. It is possible to get satisfactory results with each type but it is essential that the patient has a reasonable expectation.

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Experience with Penile Fractures in Saudi Arabia

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Summary—Seven patients with penile rupture were treated surgically within a 9-month period. All were operated on as emergencies, with successful results, except in 1 case which was associated with urethral rupture. Sexual performance was satisfactory in 6 of 7 cases.

Penile rupture (more commonly known as penile fracture) is an unusual and rare urological emergency. The true incidence is not known but 110 cases were reported in the literature up to 1983 (Nicolaisen *et al.*, 1983). Four were reported over a 9-year period by Meyer and Heinz (1984). Associated urethral injury was reported in between 10 and 22% of cases (Sant, 1981; Nicolaisen *et al.*, 1983). We have seen 7 cases in an 11-month period. The cause for such a high incidence in this region is hard to explain.

Penile rupture occurs as a result of a tear in the tunica albuginea surrounding the erectile corpora cavernosa in an erect penis during sexual activity. Characteristically all patients hear a cracking sound associated with sharp pain followed by flaccidity, swelling, deformity and discolouration of the penis.

Patients and Methods

Seven patients with penile rupture were seen in the King Khalid Hospital, Hail, between April 1987 and February 1988. A history was taken, particularly a detailed account of the incident and the time lapse to presentation (Table 1). Local examination noted the severity and extent of penile haematoma, the side of penile curvature and signs of blood at the external meatus. All patients underwent an emergency operation.

At operation, urethrography and cavernosography were performed in 2 cases only. The penis was explored through either a longitudinal or a circular

Table 1 Details of Incident

Case no.	Age (years)	Circumstance in which injury occurred	Time interval between injury and presentation (h)	Voiding problems
1	30	Sexual dream	22	No
2	60	Coitus	17	No
3	50	Coitus	20	No
4	55	Coitus (hitting the floor)	11	No
5	45	Coitus	15	Yes
6	35	Coitus	3	No
7	65	Fell on erect penis	6	No

subcoronal incision. In all patients the tunica albuginea of the corpora cavernosa was torn but the corpus spongiosum was involved in only 1 patient with urethral rupture. All but one of the tears occurred in the lateral aspect of the corpora cavernosa (Table 2). This was repaired with continuous vicryl sutures. The urethra was examined for any sign of injury. The penile haematoma was drained by multiple skin incisions and radon drain. A urethral catheter was inserted for 2 or 3 days. Prophylactic antibiotics were also used but anti-inflammatory drugs or stilboestrol to inhibit the penile erection were not required.

Results

The patients were between 30 and 60 years of age and were all sexually active. The average time to presentation was between 10 to 20 h, which may be

Table 2 Details of Injury

Case no.	Incision	Site of injury	Associated injury	Complication	Period of follow-up (months)
1	Longitudinal	Left dorsolateral 1-cm tear at root of penis	No	No	6
2	Longitudinal	Right dorsolateral 0.5-cm tear 4 cm proximal to corona	No	No	Did not attend
3	Longitudinal	Ventral 0.1-cm tear 2 cm proximal to corona	No	No	3
4	Longitudinal	Right dorsolateral 0.5-cm tear 1 cm proximal to corona	No	No	3
5	Circular	Left dorsolateral 4-cm tear 6 cm proximal to corona	No	No	6
6	Circular	Left posterolateral 1-cm tear 3 cm proximal to corona	Urethral rupture in 2 places	Wound infection, urethral stricture, skin necrosis	3
7	Circular	Right dorsolateral 1-cm tear, 3 cm proximal to corona	No	Skin necrosis	3

due to the long distance travelled, social attitude and perhaps embarrassment at being seen with this condition. The majority of the patients had no difficulty in passing urine except in the man with a ruptured urethra.

All patients were operated upon immediately. The average period of hospital stay was 9 days. In all 4 cases where a longitudinal incision was used, wound healing was uncomplicated but skin necrosis occurred on the ventral aspect near the coronal sulcus in cases where a circular incision was used. Wound infection occurred in one case in spite of routine prophylactic antibiotics.

It was possible to see 6 patients at follow-up after 6 and 12 weeks. The penile appearance was normal in all. Five patients had normal sexual function and were completely satisfied with the result.

Discussion

Penile rupture is an unusual urological injury which is easy to diagnose but treatment is rather controversial. We have no experience of conservative treatment (which has been advocated in earlier reports and includes Foley catheters, pressure dressings, ice packs, sedatives, anti-inflammatory drugs, etc), but complications were reported in 10% of the cases (Sant, 1981).

Early surgical management of penile rupture has been advocated by many authors (Sant, 1981;

Bergner *et al.*, 1982; Dever *et al.*, 1983; Nicolaisen *et al.*, 1983; Kailash and Young, 1984; Naraynsingh and Raju, 1985) in order to achieve good results, reduce the length of hospital stay and prevent penile deformity.

We used cavernosography and urethrography in 2 of our patients pre-operatively to demonstrate the site of the tear in the tunica albuginea and urethral rupture in 1 patient. Cavernosography is a simple procedure which can be performed easily on the operating table without the need for sophisticated equipment. Pre-operative cavernosography has been strongly recommended by Grossman *et al.* (1982) and Dever *et al.* (1983), to demonstrate the site of the injury and to help in planning the surgical approach.

We also recommend routine pre-operative urethrography to demonstrate any urethral injury and its site.

The surgical approach by a subcoronal circumferential incision is used by Sant (1981) and Nicolaisen *et al.* (1983), while Naraynsingh and Raju (1985) recommend direct incision at the site of injury, which can be easily identified by palpating the shaft of the penis between thumb and index finger (rolling sign). We were unable to identify the site of injury pre-operatively in any of our patients, probably due to their late presentation and widespread penile haematoma.

We used a dorsal longitudinal incision in our first

4 patients and circumferential incision in the 3 later cases. Longitudinal incision gives satisfactory access and good wound healing but the scar is less acceptable cosmetically. Circumferential incision gives good access but we found skin necrosis on the ventral surface near the glans corona in all 3 of our patients. This complication has not been described previously. Perhaps the extensive haematoma and retraction of the whole penile skin compromises the vascularity of the distal part of the penile skin, which is the most common site of necrosis.

In all 7 cases of penile rupture the tear in the tunica albuginea was unilateral and transverse, involving less than half of the circumference of the corpus cavernosum. A tear can occur in any part of the penile shaft but is most frequently found in the distal third of the penis (Narayansingh and Raju, 1985).

All 7 cases of penile rupture were managed by early surgical treatment with good results, confirming the need for immediate surgical repair of the ruptured corpus cavernosum. We also recommend pre-operative cavernosography and urethrography to demonstrate the site of the tear in the tunica albuginea and any associated urethral injury.

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Bladder Compliance in Myelodysplastic Children: Effect of Anti-reflux Surgery and Conservative Treatment

PAEDIATRIC UROLOGY

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Summary—Little is known about changes in bladder compliance and bladder capacity in myelodysplastic patients following anti-reflux surgery. A study group of 70 patients was divided as follows: group A included 20 myelodysplastic patients who had been operated on for reflux and whose subsequent treatment was conservative. Group B comprised 31 myelodysplastic patients who had been treated conservatively; a third group of 19 non-myelodysplastic patients, treated by anti-reflux surgery because of primary reflux, formed the control group. The follow-up period for group A averaged 61 months (extending from a urodynamic study 3 months after surgery to the most recent test). In group B the mean follow-up period between the initial test and the latest test was 86 months.

Bladder compliance in group A patients did not increase significantly (from 5.5 to 6.9), but patients in group B did show a significant increase (from 5.9 to 10.7). Compliance in the 19 non-myelodysplastic patients decreased only marginally 6 months after surgery (from 29.6 to 26.3). Changes in bladder capacity showed a similar trend. In their most recent test, however, the bladder capacity of group A patients increased to the same volume as that of group B. A high correlation between radiological bladder deformity and bladder compliance was found. We propose a bladder compliance of 10.0 as the lower limit for myelodysplastic patients' preferred range.

It was concluded that anti-reflux operations prevent any improvement in bladder compliance (but not in bladder capacity) compared with conservative treatment.

Bladder compliance reflects both stiffness of the detrusor muscle and sphincter competence. This relatively new concept is of prime importance in the valuation of bladder function and/or the prevention of ureteric reflux, urinary incontinence and deterioration of renal function in the neurogenic bladder. In myelodysplastic patients, reflux is present in 16 to 35 % of cases (Gaum *et al.*, 1982; Kaplan and Firlit, 1983). There are many reports of the results of anti-reflux surgery in myelodysplasias (Belloli *et al.*, 1979; Webster *et al.*, 1986), but in none of these studies are the results discussed in terms of bladder function. We have made a retrospective study of changes in bladder function

with regard to compliance and capacity in 2 groups of myelodysplastic patients: one with reflux treated by anti-reflux surgery and the other, with or without reflux, treated conservatively. An attempt was made to establish whether or not anti-reflux surgery would prevent any improvement in bladder compliance and capacity when compared with conservative treatment.

Patients and Methods

Over the past 18 years we have treated 178 patients with myelodysplasia, 72 of whom had reflux (40.4%) at the time of their initial urodynamic study. Of these 178 patients, 51 had considerable follow-up data and they form part of the present study. In

addition, 19 non-myelodysplastic patients, treated by anti-reflux surgery because of primary reflux, served as a control group (Table 1).

The 51 myelodysplastics were divided into 2 groups. Group A (20 patients) demonstrated reflux at their first investigation and were subsequently instructed to perform clean intermittent catheterisation. Depending on their clinical symptoms (*e.g.* severity of reflux, recurrent urinary infection and magnitude of renal scarring), they underwent surgery for reflux an average of 18 months later (range 1–64). The ureteric crossover method (Kondo and Otani, 1987) was used in 17 cases and Cohen's method (Cohen, 1975) in 3. Surgery failed in 2 patients: grade IIa reflux recurred unilaterally in one and unilateral ureteric obstruction required a nephrostomy tube in the other. Post-operatively they have been put on clean intermittent catheterisation. Seven of the 20 patients (35%) now have socially acceptable continence. Group B consisted of 31 myelodysplastics, 30 of whom were managed conservatively by means of clean intermittent catheterisation; 1 patient voided with detrusor contraction assisted by slight abdominal strain. Of the 31 patients, 13 had reflux in 20 ureters (low grade reflux in 16 ureters and high grade in 4). During the follow-up period reflux disappeared in 11 ureters, was downgraded in 5, upgraded in 2 and persisted in 2. Socially acceptable continence was attained in 20 patients (64%).

Pharmacotherapy was used in both groups when appropriate. Anticholinergics were given to 5 patients when urodynamic tests showed violent involuntary detrusor contractions with or without low bladder compliance. Antimicrobials were prescribed for a period of 4 weeks when the patients were instructed to perform clean intermittent catheterisation for the first time. If significant pyuria and/or overt urinary tract infection occurred,

administration of antimicrobials was also necessary. In principle, we refrained from giving these drugs for a long period of time for fear of latent adverse effects.

Urodynamic studies were performed together with intermittent fluoroscopic monitoring while the patient sat on a commode. After removal of residual urine by means of an 8 or 10 F double-lumen catheter inserted into the urethra, 30% contrast medium was slowly infused (20–40 ml/min). When leakage occurred around the catheter, or detrusor pressure increased to more than 70 cm of water, the infusion ceased. If the detrusor pressure fell too promptly after stopping the infusion, a few minutes were allowed to elapse until it had stabilised. Bladder compliance was measured by calculating the ratio of bladder capacity over detrusor pressure ($\Delta V/\Delta P$) (International Continence Society, 1981). The first examination was carried out a few weeks after the initial visit, except in infants less than 2 years old, and was repeated more than 3 times, including the initial test and the most recent: an average of 3.9 studies in group A patients and 3.5 in group B. The study 3 months after surgery was obligatory for all group A patients. In order to assess the effect of surgery on bladder compliance and bladder capacity in this group, any changes were compared using the value obtained 3 months after surgery and that observed at the most recent test (an average time span of 61 months (range 12–92)). Bladder compliance and capacity in group B were compared using the initial test and the most recent, the latter taking place an average of 86 months later (range 23–142). When major operations other than anti-reflux surgery were necessary (*e.g.* bladder neck suspension, implantation of an artificial sphincter and bladder augmentation), bladder compliance and capacity observed after these interventions were not included in the present

Table 1 Characteristics of 51 Myelodysplastic and 19 Non-myelodysplastic Patients

	No. of patients (male/female)	Mean age—months (range)		Refluxing ureters treated surgically	
		First visit	At time of operation	Grade	No.
Group A	20 (4/16)	97 (3–212)	115 (30–219)	I–IIb III–IV	11 17
Group B	31 (11/20)	90 (20–396)			
Non-myelodysplastics	19 (9/10)	100 (30–405)	105 (38–410)	I–IIb III–IV	12 22

study. In the non-myelodysplastic group, urodynamic studies were carried out only twice: once prior to surgery and again 6 months later.

Bladder deformities seen on cystography (radiological bladder trabeculation) were evaluated at maximum capacity in the latest study and severity was graded as follows: grade 0, normal; grade 1, slight deterioration; grade 2, moderate deterioration; grade 3, severe deterioration.

Wilcoxon's paired rank test (P =two tailed) and the χ^2 test were used for statistical analysis. Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted.

Results

Changes in bladder compliance in the 3 groups are shown in Table 2. The initial bladder compliance in myelodysplastic patients (groups A and B) was significantly lower than in non-myelodysplastics ($P<0.01$), although the difference between groups A and B was not significant. The most recent study showed that bladder compliance in groups A and B was significantly different ($P<0.01$). Figures 1 to 3 illustrate the changes in compliance in the 3 groups. Anti-reflux surgery followed by clean intermittent catheterisation increased compliance only slightly during a mean follow-up of 61 months ($P>0.05$), while conservative treatment increased it significantly over an average 86-month period ($P<0.01$). In non-myelodysplastics, the decrease in compliance was not significant ($P>0.1$) and remained within the normal range 6 months after operation.

Bladder capacity (Table 3) showed no significant change in group A and the controls ($P>0.1$), but did change significantly in group B ($P<0.01$). In

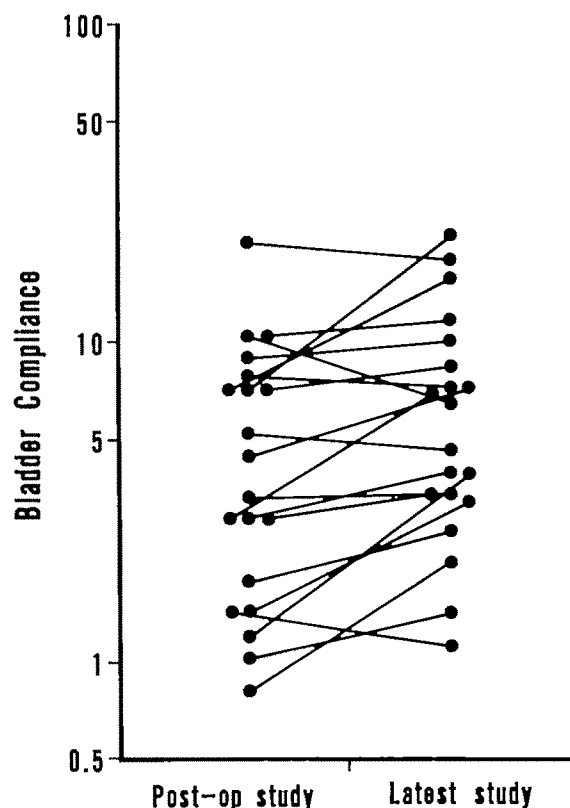


Fig. 1 Myelodysplastic patients ($n=20$) operated on for reflux and then treated by clean intermittent catheterisation (group A). The increase in compliance was not significant (from 5.5 to 6.9) ($P>0.1$). Ordinate in logarithmic scale.

general, these changes were the same as those in bladder compliance. The most recent bladder capacity in group A, however, increased to 190 ml and was almost equivalent to that of group B. Figure 4 correlates severity of bladder deformity with bladder compliance. Mean compliance was 13.3 for grades 0 and I and 5.6 for grades II and III; the difference was statistically significant ($P<0.01$).

Table 2 Changes in bladder Compliance (mean $\pm$ standard deviation).

	Bladder compliance (ml/cm of water)		
	Initial	After surgery	Latest
Group A ($n=20$)	5.1 ± 3.7	5.5 ± 4.9	6.9 ± 5.5
		$P>0.05, 61 \text{ months}$	
Group B ($n=31$)	5.9 ± 4.9		10.7 ± 8.1
		$P<0.01, 86 \text{ months}$	
Control ($n=19$)	29.6 ± 23.1	26.3 ± 12.0	
		$P>0.1, 6 \text{ months}$	

Discussion

We have retrospectively assessed the changes in bladder compliance and capacity of myelodysplastic patients over a period of several years. It could be claimed that group B should have comprised patients with reflux of the same severity as group A; this was not possible, however, for surgical decisions depend both on clinical symptoms as seen in the individual patient and on the doctor's judgement. Following an anti-reflux operation, bladder capacity will certainly decrease because

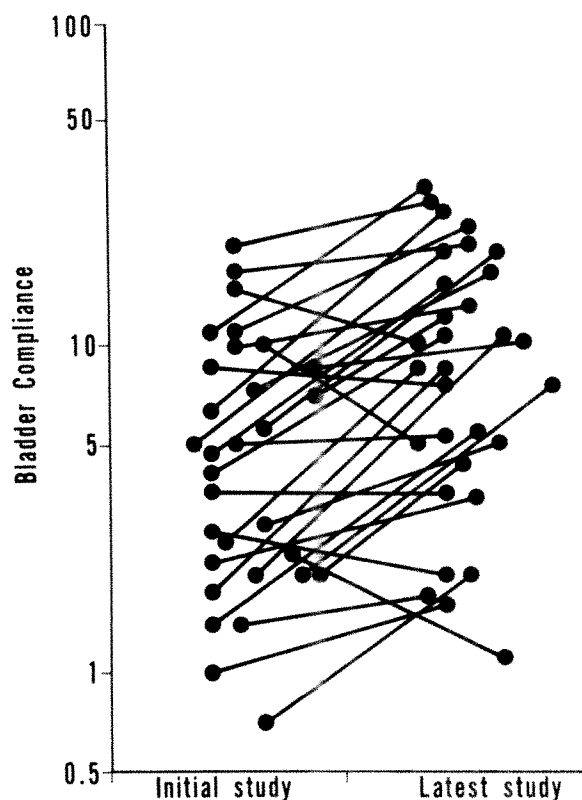


Fig. 2 Myelodysplastic patients ($n = 31$), with or without reflux, treated conservatively (group B). Bladder compliance increased significantly from 5.9 to 10.7 ($P < 0.01$). Ordinate in logarithmic scale.

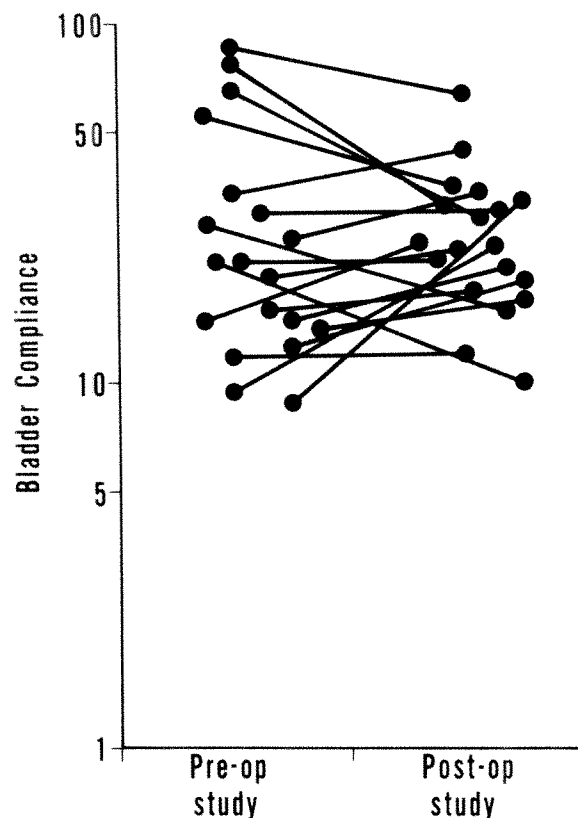


Fig. 3 Non-myelodysplastic patients ($n = 19$) operated on for reflux. The decrease in compliance was not significant (from 29.6 to 26.3) ($P > 0.1$). Ordinate in logarithmic scale.

urinary volume which is refluxed into the upper urinary tracts is eliminated. Consequently, changes in bladder compliance and bladder capacity in group A were compared by using the values observed 3 months after surgery and those at the latest test. Anticholinergics have been administered more or less continuously to 2 patients in group A (10%) and 3 patients in group B (10%). Since these patients constitute only a small fraction of each group, we believe that the drug regimen did not influence the most recent values of bladder compliance and bladder capacity, and that comparison of these values is valid.

Analysis clearly indicated that the surgically treated bladder failed to increase in compliance and that, in contrast, bladders which were conservatively treated did show a significant increase (Table 2). Bladder compliance is affected by several factors such as natural physical growth, the effect of clean intermittent catheterisation, pharmacotherapy, recurrent urinary infection, sphincter incompetence and the stiffness of the detrusor muscle.

Since these common denominators (apart from stiffness of the detrusor) were shared equally by both groups A and B, they cannot explain the difference in bladder compliance. Furthermore, bladder compliance in an initial urodynamic study was not significantly different between the 2 groups.

Table 3 Changes in Bladder Capacity (mean $\pm$ standard deviation)

	Bladder capacity (ml)		
	Initial	After surgery	Latest
Group A ($n = 20$)	(139 $\pm$ 82)	171 $\pm$ 78	190 $\pm$ 70
		$P > 0.1$, 61 months	
Group B ($n = 31$)	140 $\pm$ 61		197 $\pm$ 73
		$P < 0.01$, 86 months	
Control ($n = 19$)	224 $\pm$ 68	235 $\pm$ 98	
		$P > 0.1$, 6 months	

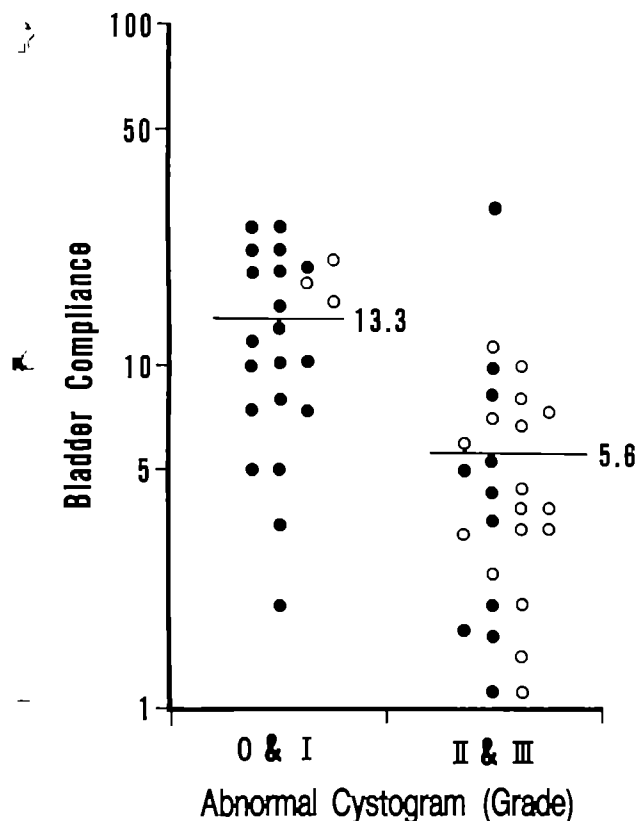


Fig. 4 Significant correlation between severity of cystographic deformity and bladder compliance in 51 myelodysplastics ($P < 0.01$). Mean compliance was 5.6 for grades II and III and 13.3 for grades 0 and I. ○ = group A, ● = group B. Ordinate in logarithmic scale.

The only factor unique to group A was that all patients had undergone surgery for relief of reflux. Although we have no histological evidence, it is possible that surgery aggravated fibrotic changes in the detrusor muscle. Light and Pietro (1986) and Murray *et al.* (1988) observed a deterioration in detrusor hyper-reflexia and a loss of bladder compliance in several myelodysplastic patients who had undergone implantation of an artificial sphincter. These reports, together with our present findings, seem to indicate that surgical incision of the detrusor muscle or encroachment into the perivesical space will render bladders less compliant than those of the normal person and will prevent any improvement in compliance.

Bladder capacities at the initial and latest studies were not significantly different between groups A and B (Table 3). This would indicate that, irrespective of treatment, bladder capacity increases to around 190 ml over an average time span of 5 to 7 years. Examining bladder capacity in isolation may

be misleading, since compliance is an important factor in bladder function. For example, both urinary continence and bladder deformity are closely related to bladder compliance. Socially acceptable continence has been attained in 35% of group A patients (7/20) and 64% of group B patients (20/31)—a significant difference ($P < 0.05$). Bladder deformity as seen on the cystogram was also correlated significantly with bladder compliance (Fig. 4): in patients with higher compliance the bladders appeared more normal on X-ray. In 1956 when clean intermittent catheterisation was unknown, Morales *et al.* (1956) found that 25 of 34 myelodysplastics (74%) had moderately or markedly trabeculated bladders. Their data suggest that voiding by abdominal straining or the Credé manoeuvre, neither of which is now recommended (Action Committee on Myelodysplasia, 1979), aggravated trabeculation by means of high intravesical pressure together with residual and recurrent urinary infection.

There is no definition of the normal range of bladder compliance in spina bifida patients. As a result of our present findings and our experience with many myelodysplastics, we propose that a bladder compliance of 10.0 be taken as the lower limit of the preferred range (there is, of course, no upper limit). This value coincides with a ratio of bladder capacity over detrusor pressure of 10:1; for instance, 200 ml/20 cm of water or 300 ml/30 cm of water. There were 20 patients (5 in group A and 15 in group B) whose bladder compliance exceeded this lower limit. The fact that 17 of these 20 patients (85%) became continent supports the validity of our proposal.

Despite anti-reflux surgery, 5 patients in group A eventually attained high compliances of over 10.0 and socially acceptable continence. The common symptoms of those patients before surgery are worth considering, since they are useful in deciding on treatment. They include a rather large cystometric capacity of 250 ml (range 200–340), absence of symptomatic urinary infection, and normal renal function. Bladder compliance at the initial test was not a factor, since it varied from 2.7 to 12.2. Patients who fulfil these criteria have a good chance of attaining a compliant detrusor post-operatively. For those who do not, we recommend treatment with a teflon paste injection at the periureteric orifice (Puri and Guiney, 1986) or a conventional anti-reflux operation combined with bladder augmentation.

In conclusion, it was found that anti-reflux surgery prevented an increase in compliance, while

conservative treatment resulted in significantly higher compliance. Although bladder capacity at the most recent study did not differ significantly between groups A and B, it was bladder compliance, not capacity, that regulated urinary continence and deformity of the bladder.

Acknowledgements

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Case Reports

Spontaneous Rupture of Splenomegaly due to Disseminated Bone Metastases from Prostatic Carcinoma

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Case Report

A 76-year-old patient was treated with radiotherapy (60 Gy) for locally confined, well differentiated prostate adenocarcinoma. He made satisfactory progress for 18 months but biochemical progression, consisting of a progressive increase in prostate acid phosphatase (PAP) and prostate specific antigen (PSA), was then noted; there were no subjective complaints. No treatment was given. A few weeks later the patient was readmitted with generalised deterioration and fever resistant to broad spectrum antimicrobial therapy.

There was no radiological evidence of metastatic disease, although anaemia (haematocrit 30%), hyperleucocytosis (31,900 white blood cells) and increased prostate tumour markers were found. Over a 4-month period the PAP levels increased 3-fold (54 u/l), alkaline phosphatase 6-fold (1190 u/l) and PSA levels exceeded 100 ng/ml. The haemogram showed a leucoerythroblastic formula (4% normoblasts, 7% myelocytes and 3% metamyelocytes), indicating extramedullary haematopoiesis. Bone marrow puncture in the sternum revealed massive tumour invasion by an adenocarcinoma (Figs 1 and 2). The bone cortex and trabeculae were intact, which explained the absence of radiological lesions. Before a bone scan could be done the patient suddenly collapsed and died. Autopsy showed rupture of an enlarged spleen (520 g), PSA-positive bone marrow metastases and signs of extramedullary haematopoiesis in the spleen.

Comment

Although biochemistry, haematology and autopsy indicated the presence of bone metastases, X-ray exploration of the skeleton was negative. This is in accordance with earlier reports (Welsh and McKinney, 1964; Mehan *et al.*, 1966; Willis, 1973), where bone metastases were shown to appear first in the bone marrow, which cannot be diagnosed with conventional radiological imaging. A bone scan would have given more information.

The bone marrow metastases can give rise to myelophthisis with subsequent extramedullary haematopoiesis. This can lead to splenomegaly, which in our patient was complicated by spontaneous rupture.

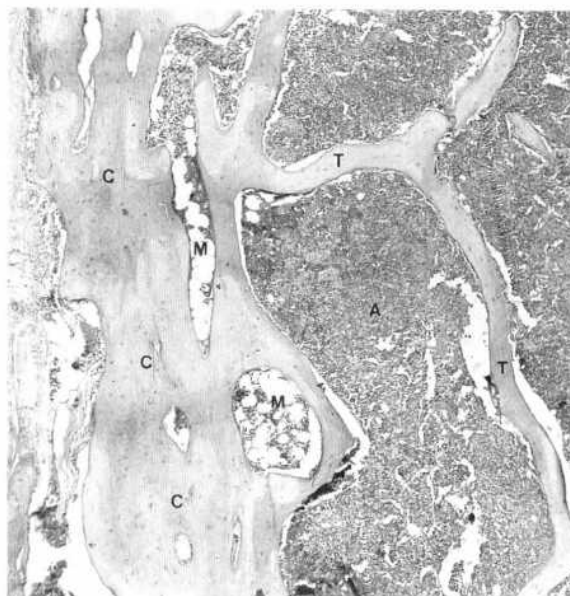


Fig. 1 Bone biopsy showing intact bone cortex (C) and bone trabeculae (T). The haemopoietic marrow is largely replaced by metastatic adenocarcinoma (A) with very little marrow being preserved (M). (H and E $\times 10$).

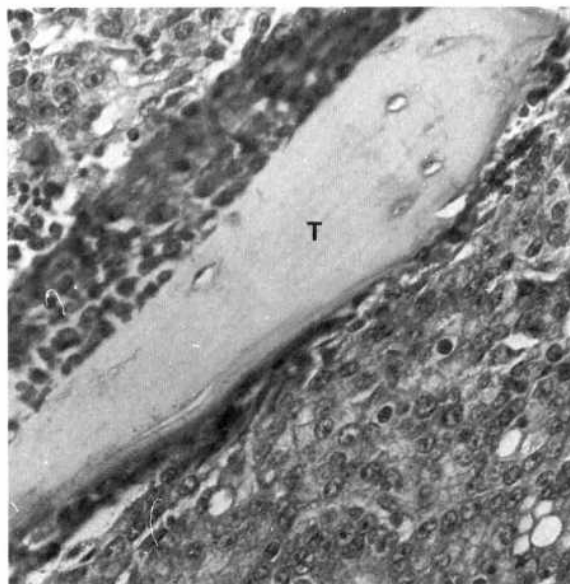


Fig. 2 Intact bone trabecula (T) surrounded by massive adenocarcinoma with acinar architecture and prominent nucleoli. (H and E $\times 62.5$).

When signs of bone marrow invasion are present in a patient with metastatic prostate cancer, hormonal treatment should be advised promptly.

Bone scan is the examination of choice in the follow-up of prostate cancer patients. Ultrasonographic estimation of the splenic volume can be useful.

The possibility of widespread bone marrow invasion with sudden death due to splenomegaly could be an argument in favour of early hormonal therapy.

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Xanthogranulomatous Pyelonephritis with Nephrocutaneous Fistula at the Knee

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The case involves a xanthogranulomatous pyelonephritis (XGP) with a homolateral nephrocutaneous fistula at the knee. The case's interest lies in the unprecedented length of the fistula (Parson *et al.*, 1986).

Case Report

A 70-year-old female patient with a previous history of arterial hypertension and 2 strokes was brought to the emergency ward with a 1-month history of continuous fever, asthenia and pain in both the pelvic area and the

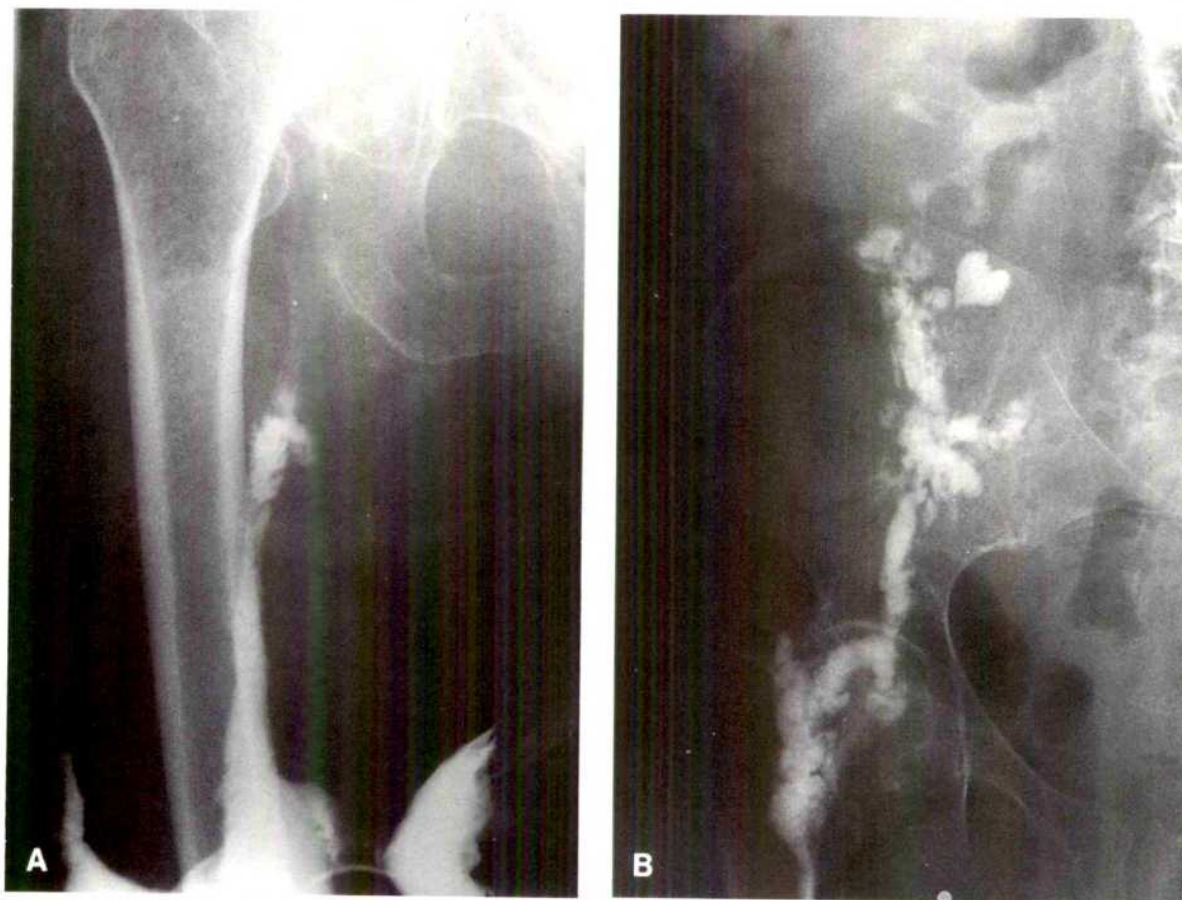


Fig. Fistulography showing the nephrocutaneous communication from knee (A) to kidney (B).

right thigh. On exploration an abscess with soft tissue destruction was found on the lower third of the right thigh. The general analysis showed leukocytosis, ESR of 85 mm and anaemia with hypochromia. Renal and hepatic function yielded normal results. The abscess was drained; a culture of *Proteus mirabilis* was obtained. IVU revealed right-sided renomegaly with staghorn lithiasis and a non-functioning kidney. Fistulography taken through one of the knee openings showed a path ascending all the way to the right kidney (Fig.).

The patient underwent right side nephrectomy through a posterolateral lumbotomy and removal of the 12th rib. Post-operative recovery was normal and the fistula closed spontaneously in a few days. Pathological examination confirmed the existence of XGP with a subsequent affection of perirenal tissue and the psoas muscle.

Comment

XGP frequently appears in association with renal lithiasis and chronic infection (Malek *et al.*, 1972). It can be situated in the calices or renal parenchyma or extend into the perirenal area, affecting other organs such as the colon, duodenum, liver, spleen, diaphragm, bronchi or abdominal wall, with the possibility of causing a cutaneous fistula (Malek *et al.*, 1972; Fernandez *et al.*, 1989).

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Calcified Hydronephrosis and Pelviureteric Junction Obstruction

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Case Report

A 15-year-old white male presented with a recent history of blood in his urine. He had a past history of microscopic

haematuria that was not associated with either trauma or infection. On physical examination his abdomen was normal and he had a left varicocele, with normal sized testes. An abdominal X-ray showed a right upper quadrant abdominal mass (Fig. 1). A CT scan demonstrated a large left kidney with normal anatomy. A calcified rim of tissue surrounding a cystic mass was identified in the right upper quadrant (Fig. 2). Retrograde pyelography confirmed a right pelviureteric junction obstruction.

A right flank nephrectomy was performed and 300 ml of chocolate-coloured substance were aspirated from the kidney. The fluid was found to be negative for malignancy but pathological examination showed severe hydronephrosis, pelviureteric atresia and calcified old haemorrhage.



Fig. 1 IVU demonstrates eggshell calcification of right renal mass.

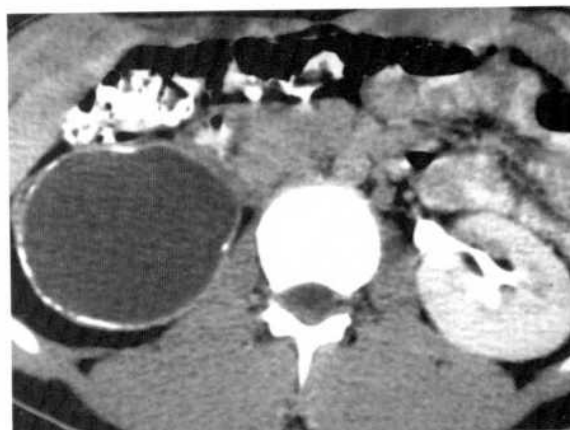


Fig. 2 CT demonstrates calcified rims.

Comment

The significance of calcified renal masses has been controversial. Daniel *et al.* (1972) concluded that eggshell calcification generally represented a benign cyst; however, the risk of malignancy in such lesions is 20%. They described no calcifications secondary to hydronephrosis. A recent review of calcified renal masses by Patterson *et al.* (1987) showed that 20% cannot be easily characterised as benign or malignant by CT scan. They strongly recommended surgical exploration of the mass because 40% may be malignant.

Hydronephrosis with calcification and pelviureteric junction obstruction is rare. O'Reilly (1986) showed that chronic dilatation in hydronephrosis is known to bleed, as was true in our case. Extensive dilatation probably produced chronic intermittent haemorrhage with progressive calcification of renal tissue.

To our knowledge, there is no report of calcified hydronephrotic kidney in the paediatric population.

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Pelvic Lipomatosis

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Pelvic lipomatosis is a rare disease in Caucasians. We describe a patient who presented originally with bladder outlet obstruction and later developed vesicoureteric obstruction.

Case Report

A 48-year-old Caucasian male of normal body habitus presented with a 1-week history of left loin pain. Intravenous urography (Fig. 1) showed gross hydro-

ureterectasis and a significant residual volume after micturition. Renal function was normal biochemically. DTPA renography showed prompt but incomplete clearance of isotope from the upper tracts. Urodynamic assessment showed a micturition pressure of 150 cm H₂O and a mean flow of 10.2 ml/s. Cystoscopy revealed bladder neck stenosis and cystitis glandularis. A bladder neck incision was performed to good effect. The patient remained biochemically and radiographically stable over a 3-year follow-up period, at which time the left loin pain recurred. Intravenous urography was essentially normal as before. Antegrade ureterography demonstrated tapering of the ureters at the vesicoureteric junction (Fig. 2). Manometry performed at the same time showed a mean pressure of 34 cm H₂O in the renal pelvis compared to a resting intravesical pressure of 22 cm H₂O. This time cystoscopy revealed an exceptionally long posterior urethra and cystitis glandularis; the ureteric orifices were not identifiable. Intravenously injected indigo carmine appeared in the urine 2 h later. At this stage it was decided to reimplant the ureters. At operation the ureters were encased in fatty tissue and the bladder was pushed out of the pelvis by an abundance of fat. Histology was consistent with pelvic lipomatosis. Post-operative recovery was uneventful apart from a brisk post-operative diuresis.



Fig. 1 Intravenous urogram showing grossly dilated and tortuous ureters and excessive soft tissue interposition between bladder and pelvis.



Fig. 2 Antegrade ureterogram showing tapering of ureter at vesicoureteric junction.

Comment

Pelvic lipomatosis is a rare benign disease affecting mainly black males. There are approximately 30 case reports in the literature of the condition affecting Caucasians (Klein *et al.*, 1988). The aetiology is unknown and no definitive therapy has been described. The most serious manifestation of this disease is progressive urinary obstruction at either the vesicoureteric or bladder outlet level resulting in renal failure. Consequently, urinary diversion may ultimately be necessary.

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Ileocaecal Intussusception due to Metastatic Renal Carcinoma

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Intussusception is the telescoping of a segment of bowel into an adjacent area. It usually occurs in

children with a peak incidence at 4 years. When intussusception occurs in adults it is predominantly associated with a lead point. In the present case, intussusception was due to metastatic renal tumour.

Case Report

In 1982 the patient had a left nephrectomy for renal carcinoma. In 1985 the upper lobe of his right lung was resected for metastasis. He developed recurrent haematuria in 1988 and was found to have a large right renal carcinoma. In 1989 he developed acute abdominal pain. Plain abdominal X-rays revealed a small bowel obstruction which settled on conservative management but recurred 3 months later. Barium studies and CT scan showed a mass within the caecum (Fig.). Laparotomy revealed an ileocaecal intussusception with a polypoid tumour of the ileum at its apex. This was resected. Histology demonstrated a metastasis from a renal tumour. He made a good recovery from this operation but his general condition deteriorated and he died 3 months later.



Fig.

Comment

Secondary tumour of small bowel is rare. Obstruction usually occurs because of kinking or encroachment of the lumen (Smith *et al.*, 1977). Intussusception is uncommon with a secondary tumour. To our knowledge this is the first reported case of ileocaecal intussusception due to renal tumour, although single cases of small bowel intussusception have been reported (Haynes *et al.*, 1986).

Diagnosis of this condition is difficult and there is often delay (Fawaz and Hill, 1983). Intussusception due to intramural metastasis is rare but should

be considered as a cause of obstruction, particularly when the symptoms are intermittent or recurrent.

Acknowledgements

I thank Mr W. O. Thompson for his permission to present this case. I am also grateful to Mr G. Sunderland and the Radiology Department of Hairmyres Hospital and Stobhill Hospital for their assistance.

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Arteriovenous Malformations of the Ureter and Bladder. A Fatal Case of Haematuria

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Acute exanguinating haemorrhage from large bowel angiodysplasia is a well reported phenomenon, with some centres claiming it to be the causal factor in as many patients as that from diverticular disease (Ford, 1981; Howard *et al.*, 1982). The mortality rate from lower gastrointestinal haemorrhage for all causes is 10% (Way, 1983). We report a case of fatal haematuria caused by arteriovenous malformations involving the right ureter and the bladder.

Case Report

A frail 87-year-old woman was referred with a 1-week history of painless haematuria. When seen at the initial consultation the haematuria had subsided and she had no other symptoms, but her haemoglobin was 7.7 g/dl, white cell count $6.3 \times 10^9/l$ and platelet count $371 \times 10^9/l$.

She was admitted for transfusion and further investigation. An IVU revealed a normal left kidney and ureter but no opacification of the right collecting system. A large filling defect, consistent with a blood clot, was noted in the bladder. The patient was unfit for general

anaesthesia and flexible cystoscopy was therefore performed. The view was obscured by a large blood clot in the bladder but clot was observed issuing from the right ureteric orifice. Retrograde ureterography was normal.

The haematuria recurred, the patient developed clot retention and required a further blood transfusion. Ultrasound examination of the bladder showed a mild right-sided hydronephrosis with a large clot in the bladder. Renal angiography revealed no abnormality. Unfortunately, the patient developed acute pulmonary oedema during the course of the repeated transfusions, despite diuretic cover, and this proved to be fatal.

At autopsy the patient was found to have atheromatous coronary arteries with evidence of a previous myocardial infarction. The right kidney was enlarged with dilatation of the calices and ureter, the appearances being suggestive of a subacute hydronephrosis. There was a raised haemorrhagic area with adherent blood clot in the right ureter.

The left kidney was entirely normal. The bladder was filled with clot, with some superficial petechiae related to catheter trauma. Between the ureteric orifices was a pedunculated lesion measuring 1.5×1.0 cm. Histology of this lesion and the haemorrhagic lesion in the right ureter was that of an arteriovenous malformation with overlying thrombus (Fig.).

Comment

Arteriovenous malformations of the renal parenchyma are well described (Yoshiki *et al.*, 1987). Other arteriovenous malformations such as those which erode the ureter and cause profuse haema-

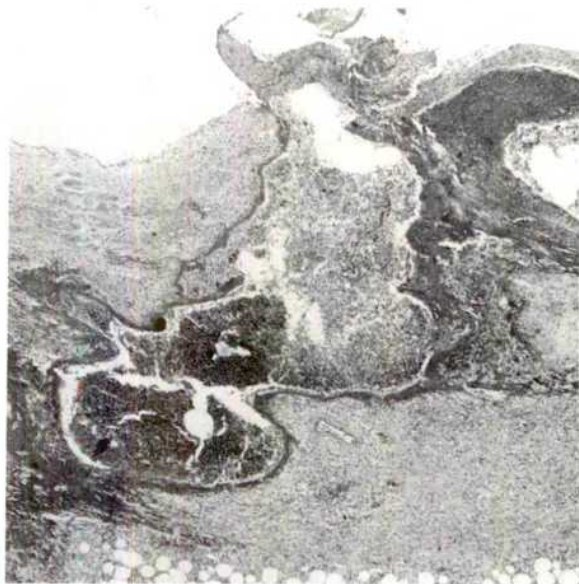


Fig. Section through the bladder wall showing dilated, tortuous blood vessels and overlying thrombus, consistent with an arteriovenous fistula (Elastic Van Gieson stain).

turia have also been described (Sharma *et al.*, 1988). The diagnosis was missed in our patient because she was never fit for effective clot evacuation, even under regional anaesthesia, and the arteriovenous malformation in the bladder was hidden by clot. Biopsies of arteriovenous fistulae are often inconclusive and in this case could have exacerbated the haemorrhage, although it may have been possible to coagulate the lesion with the roly-ball diathermy. The renal angiogram was unhelpful in this case because the vessels supplying the malformations in the bladder and ureter would not have been filled from the renal vessels.

As far as we are aware, primary arteriovenous malformations of the ureter and bladder leading to profuse and fatal haematuria have not been described.

Acknowledgement

We thank Professor J. P. Blandy for allowing us to study his patient.

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Lymphocele following Renal Graft Trauma

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Case Report

A 35-year-old male suffering from end-stage glomerulonephritis received a cadaveric renal transplant in August

1978. The graft was placed in the right iliac fossa using conventional surgical technique. The patient was discharged 4 weeks later with normal graft function (creatinine 1.6 mg%). Creatinine remained stable at regular follow-up. In December 1983 he was rehospitalised with a painful swelling over the graft, which developed 2 days after he had sustained a violent blow to this region while logging. Creatinine increased to 2.4 mg%; the patient was normotensive and afebrile. Ultrasonography revealed a large collection of fluid surrounding the graft (Fig.). Severe pain prompted exploration: 800 ml of clear yellowish fluid were evacuated and some blood clots were removed from the surface of the completely decapsulated kidney, causing diffuse bleeding. Haemostasis was achieved by electrocoagulation and a drain was inserted; 1 L of clear fluid (sodium 136 mmol/l, potassium 3.7 mmol/l, chloride 115 mmol/l, protein 0.7 g%) was drained over 2 days; a wide fenestration between the renal capsule and the adjacent peritoneal cavity was created. This was followed by an immediate return to normal of all functional parameters. The lymphocele, however, recurred in December 1988 accompanied by a slight increase in serum creatinine (2.25 mg%). At surgery the first fenestration turned out to be obliterated and a new, even wider marsupialisation was performed. Since then, the patient has been symptom-free without evidence of recurrence and with good graft function.

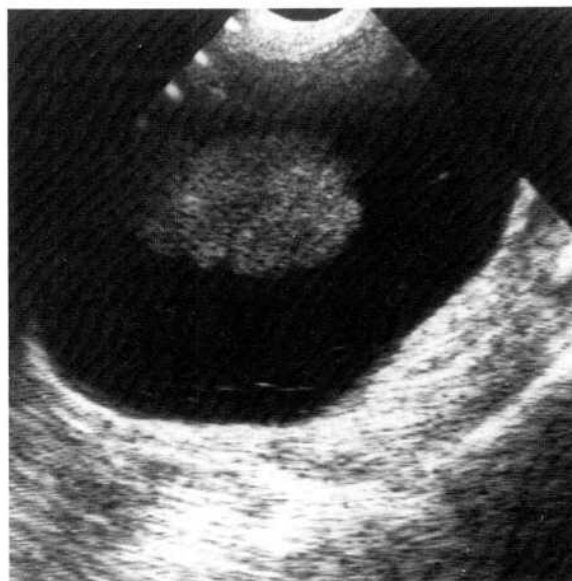


Fig. Transverse real time ultrasonography image showing extensive fluid collection around the graft.

Comment

Leakage of lymph fluid from the surface of a transplanted kidney is an extremely rare condition

leading to lymphocele formation (Nghiem *et al.*, 1982; Roney and Wellington, 1985; Thompson and Neale, 1989). A traumatic lymphocele, however, has been reported only once (Roney and Wellington, 1985). Local disruption of the lymphatic vessels by bleeding into the subcapsular space and further decapsulation by lymphatic leakage must be considered as the causative mechanism of this type of lymphocele. External drainage led to a massive loss of fluid, protein and electrolytes (Roney and Wellington, 1985). Internal drainage into the peritoneal cavity is advocated as the treatment of choice.

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Seeding of Transitional Cell Carcinoma within the Vagina

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Transitional cell carcinoma of the bladder is extremely common in urological practice. It is well recognised that intravesical seeding of tumour cells can lead to recurrent disease after local endoscopic resection (Soloway and Masters, 1980). It is surprising that more previous cases of local vaginal seeding of transitional cell carcinoma to the introital or vaginal mucosa have been reported.

Case Report

An 84-year-old female presented in 1971 with painless haematuria. She had had a total abdominal hysterectomy in 1956.

Cystoscopic evaluation revealed a superficial tumour of the bladder base which was resected and histological examination confirmed a G1P1 transitional carcinoma (Fig. 1). For 14 years her bladder cancer was controlled

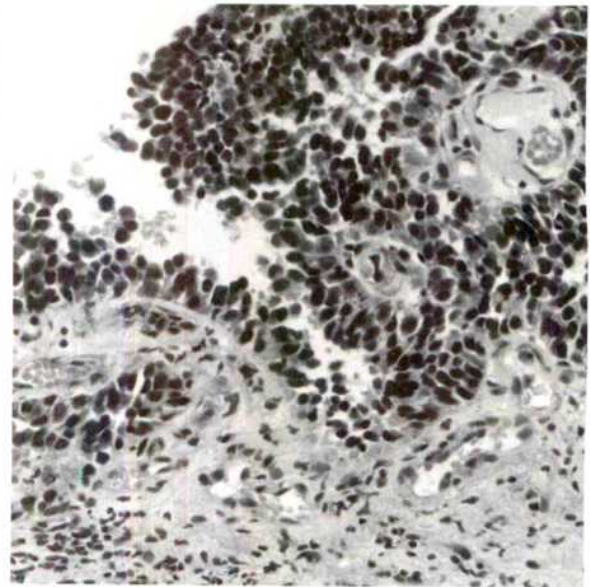


Fig. 1 G1P1 transitional cell carcinoma (1971).

by regular cystoscopy with an occasional small tumour recurrence resected or cauterised. On several occasions, however, histological examination confirmed a G2P1 transitional cell carcinoma. In 1985 she reported vaginal bleeding and examination under anaesthesia revealed induration of the anterior vaginal wall, biopsy of which was reported as poorly differentiated transitional cell carcinoma (Fig. 2). She was therefore treated with local catheter radiotherapy and followed up by regular cystoscopy and colposcopy. The bladder has been clear

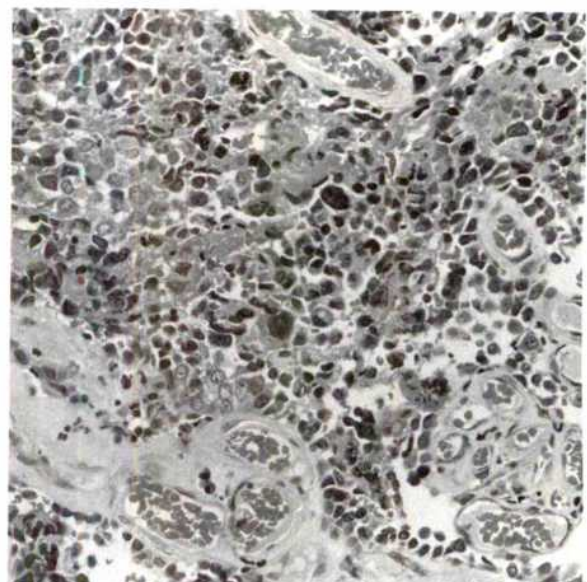


Fig. 2 Biopsy of anterior vaginal wall showing metastatic transitional cell carcinoma.

of tumour on each occasion to date, but vaginal recurrence of poorly differentiated transitional cell carcinoma was found 18 months after radiotherapy.

In view of her age she was managed by local colposcopic resection and colpodiatomy at 4-monthly intervals and 4 years from this diagnosis, her last colposcopy was clear of tumour. However, palpable inguinal lymph nodes, which on aspiration cytology were found to be involved by transitional cell carcinoma, have recently been demonstrated and local palliative radiotherapy has been arranged.

Comment

Vaginal transitional cell carcinoma following cystectomy is documented, presumably either from inadequate resection margins or spillage during operation (Chin *et al.*, 1985). We are unaware of vaginal seeding without prior open surgery or radiotherapy and we postulate that seeding via the irrigating fluid may have occurred. This provides additional support for irrigating with water instead of saline during cystoscopy for bladder cancer to increase tumour cell lysis and prevent vaginal seeding (Levin and Moskovitz, 1986).

The subsequent development of overt lymph node metastases, despite good local control of the vaginal disease, implies that this manifestation of bladder transitional cell carcinoma carries a poor prognosis.

Acknowledgements

We thank Dr M. Falzen, Department of Histopathology, and Dr G. Duchenne, Department of Radiotherapy, for their help in this report.

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Points of Technique

Ureteric Obstruction by Ligature Treated by Endoscopic Diathermy

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The incidence of ureteric obstruction after hysterectomy is 2 to 3% (Symmonds, 1966). Open surgery has so far been the method of treatment of such obstruction.

A cold coaxial knife has recently been used to treat ureteric strictures, with better short-term results than those achieved following other endoscopic procedures associated with dilatation (Selikowitz, 1990).

We present what we believe to be the first reported case where total occlusion of the ureter by ligature was successfully treated by endoscopic diathermy.

Case Report

A 35-year-old woman presented with diffuse abdominal pain, 10 weeks after a total abdominal hysterectomy.

Electrolytes, urea and creatinine were all within normal limits. CT scan revealed hydronephrosis of the left kidney.

A nephrostomy tube size 7F double pigtail catheter (Nephrofix: Cook, Bjaeverskov, Denmark) was introduced under local anaesthesia. Urine output from the left kidney was about 1 L/day. A nephrostogram was subsequently performed (Fig. 1).

Technique

Under general anaesthesia and X-ray control, contrast was injected into the nephrostomy tube to show the level of obstruction in the lower ureter. An 11.5 F ureteroscope was passed approximately 4 cm up the ureter to visualise the obstructed area. Repeat X-ray screening after the nephrostogram with the ureteroscope *in situ* suggested the stricture was short but complete.

The tip of a 4 F ureteric catheter was amputated to allow the stylet to protrude for 5 mm. The external end of the stylet was connected to a



Fig. 1

diathermy lead. The occlusion was visualised, the ureteric catheter with the bare stylet was advanced and the obstruction was incised with diathermy (Bee-Sting). No suture material was visible. The ureteroscope then passed easily into the dilated upper ureter. A double pigtail stent (Urecath: Braun, Melsungen, Germany) was then placed in position (Fig. 2). A nephrostogram showed the renal pelvis and ureter emptying easily into the bladder with a small leak of contrast at the site where diathermy was applied.

Repeat IVU 3 weeks later showed rapid emptying of the pelvis and an intact ureter. The double pigtail stent was then removed. The patient has remained well since and the ureter has not strictured. Review, including repeat IVU at 6 months, was normal.

Comment

Ureteroscopes are very effective tools in the management of ureteric calculi, especially in the lower third. To date, accidental ligature of the ureter has been managed by open surgery.

A cold coaxial knife has recently been used in the management of ureteric strictures, and it has the potential to be converted into an electrosurgical device. The introduction of such an accessory knife would be a great contribution to the management of ureteric obstruction as it would be more acceptable to the patient than other procedures, and open management may become a rarity.



Fig. 2

Attempted Transurethral Resection of Suprapubic Catheter

M. L. CROSFILL, *Department of Surgery, West Cornwall Hospital, Penzance*

The patient, a 79-year-old man, had been relieved of his acute retention by means of a Porges 12 F suprapubic catheter. This was noted at preliminary cystoscopy to lie slightly coiled in the bladder. During subsequent transurethral resection of the prostate the loop became embroiled with the catheter and could not be freed. An attempt was made to draw catheter and loop out through the urethra but this only resulted in disintegration of the loop. The shaft of the loop was withdrawn without difficulty but some of the cutting wire was seen to be missing, and on further examination this was found to transfix the shaft of the catheter into which it was fused. Catheter and wire were pulled out through the urethra using biopsy forceps, after which the resection proceeded uneventfully.

Examination of the catheter afterwards showed that the loop had cut into the plastic whilst still hot and the tract had sealed itself (Fig.).



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Requests for reprints to: D. Kiely, Department of Urology, Mercy Hospital, Cork, Republic of Ireland.

Awareness of this complication should be enough to prevent it and it might help to check that a suprapubic catheter has not been inserted further into the bladder than necessary.

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Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Glasgow. 25–28 June 1991

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Edinburgh Urological Festival

Edinburgh. 21–23 August 1991

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Edinburgh EH4 2XU.

Shackman Travelling Fellowship 1992

Applications are invited from Medical Practitioners registered in the United Kingdom who are either trainees in Urology or Organ Transplantation or Consultant Urological Surgeons or Consultant Surgeons with a major commitment to transplantation of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for application is 1 September 1991.

Further particulars and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £1000.00 for any article(s) of outstanding merit published each year (2 volumes) in the British Journal of Urology. Candidates for the prize must be Fellows of the Royal College of Surgeons in the British Isles, Canada, Australia or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to urological centres outside Britain for consideration by the adjudicators, who shall be the Chairman of the Editorial Board, the Honorary Editorial Secretary and one nominee from Council. This prize is not necessarily awarded annually.

Norwich Eaton Travelling Scholarship

The scholarship(s) will cover travel, accommodation and registration expenses associated with attending the Society of University Urological Residents and American Urological Association meetings. They will be awarded annually until such time as either the Senior Urological Registrars Group or Norwich Eaton Ltd decide not to continue and will be available to any person appointed to an accredited urological training post.

The scholarship(s) will be awarded to the person(s) presenting the winning paper at the Senior Urological Registrars Group Annual Meeting. The winning paper(s) will be selected by those members of the Senior Urological Registrars Group present at the meeting and appointed to urological training posts.

Diary

1991

- June 7-8 Fourth Pediatric Surgery Research Workshop, Berlin, Germany. Contact: Dr F. Schier, Pediatric Surgery, Univ.-Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany. Tel: (0 30) 7 98 41 81/29 09.
- June 12-15 Congress of the Portuguese Association of Urology. Funchal, Madeira Island. Contact: Dr Manuel Mendes Silva, Rua Consiglieri Pedrosa, 123, 2745 Queluz, Portugal. Tel: (351-1) 4354044/9.
- June 16-20 Canadian Urological Association Annual Meeting, Ottawa. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
- June 17-22 Diploma Course Revision Block. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
- June 18-22 Tenth World Congress for Sexology, Amsterdam, The Netherlands. Contact: Congress Secretariat, 10th World Congress for Sexology, c/o RAI Organisatie Bureau Amsterdam bv, Europaplein 12, 1078 GZ Amsterdam, The Netherlands.
- June 19-23 First World Congress of Medical Polonia, Częstochowa, Poland. Contact: Dr Zenon Rudzki, Secretary General, First World Congress of Medical Polonia, Dr Rydygier's Surgical Hospital, U1, Mirowska 25, 42-200 Częstochowa, Poland.
- June 21 Meeting of the Dutch Society of Impotence. Amsterdam, The Netherlands. Contact: Dr H. H. J. Leliefeld (President), St Laurentius, Ziekenhuis, Mgr. Driessenstraat 6, 6040 AX, Roermond, The Netherlands.
- June 25-28 BAUS Annual Meeting, Scottish Exhibition and Conference Centre, Glasgow. Contact: BAUS office.
- July 2-3 Diploma Course Examination. For further details of these courses and meetings please contact: The Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 071 240 9115.
- August 21-23 Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU.
- August 25-31 First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands.
- September 1-6 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.
- September 4-7 Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői út 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.
- September 16-19 Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China.

- September 26–27 Annual Paediatric Urology Course, Selwyn College, Cambridge. Contact: Mr R H Whitaker, Dept. of Urology, Addenbrooke's Hospital, Cambridge. Tel: 0223 216344.
- October 3–5 Annual Meeting of Swiss Society of Urology, Geneva, Switzerland. Contact: Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.
- October 4–5 Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office.
- October 9–12 1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands.
- October 10–12 International Continence Society, 21st Annual Meeting, Hannover. Contact: Guus Kramer, Chairman ICS, Department of Urology, Hannover Medical School, P.O. Box 610180, 3000 Hannover 61, Germany.
- October 18–19 Surgical Treatment of Prostatic Cancer: Comparison of Techniques. Milan, Italy. Contact: Dr F. Gaboardi, Divisione di Urologia, Ospedale Fatebenefratelli ed Oftalmico, C.so Porta Nuova 23, 20121 Milan, Italy. Tel. 0039-2-636443.
- October 20–November 4 Royal College of Surgeons of England Joint Meetings in Pakistan and India. Contact: Craig Duncan, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, WC2A 3PN.
- November 15–16 Third Biennial Asia-Pacific Meeting on Impotence, Taipei, Taiwan, R.O.C. Contact: Third Biennial Asia-Pacific Meeting on Impotence, c/o Taiwan Conference Management Co. Ltd, P.O. Box 68–439, 6F–3, 102 Chung Shan N. Road, Sec. 2, Taipei, Taiwan, R.O.C.
- 1992
- January 10 Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
- May 6–8 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
- May 10–14 American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.
- June 21–26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
- June 22–25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
- July 22–25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
- August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

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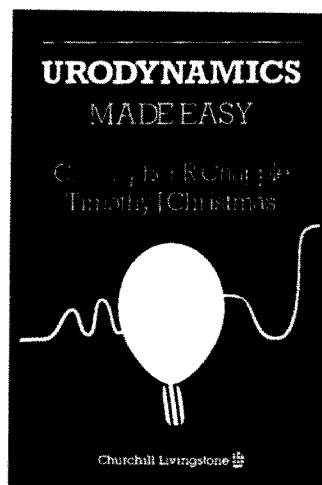
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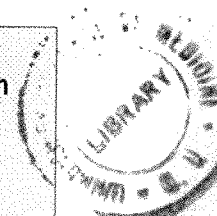
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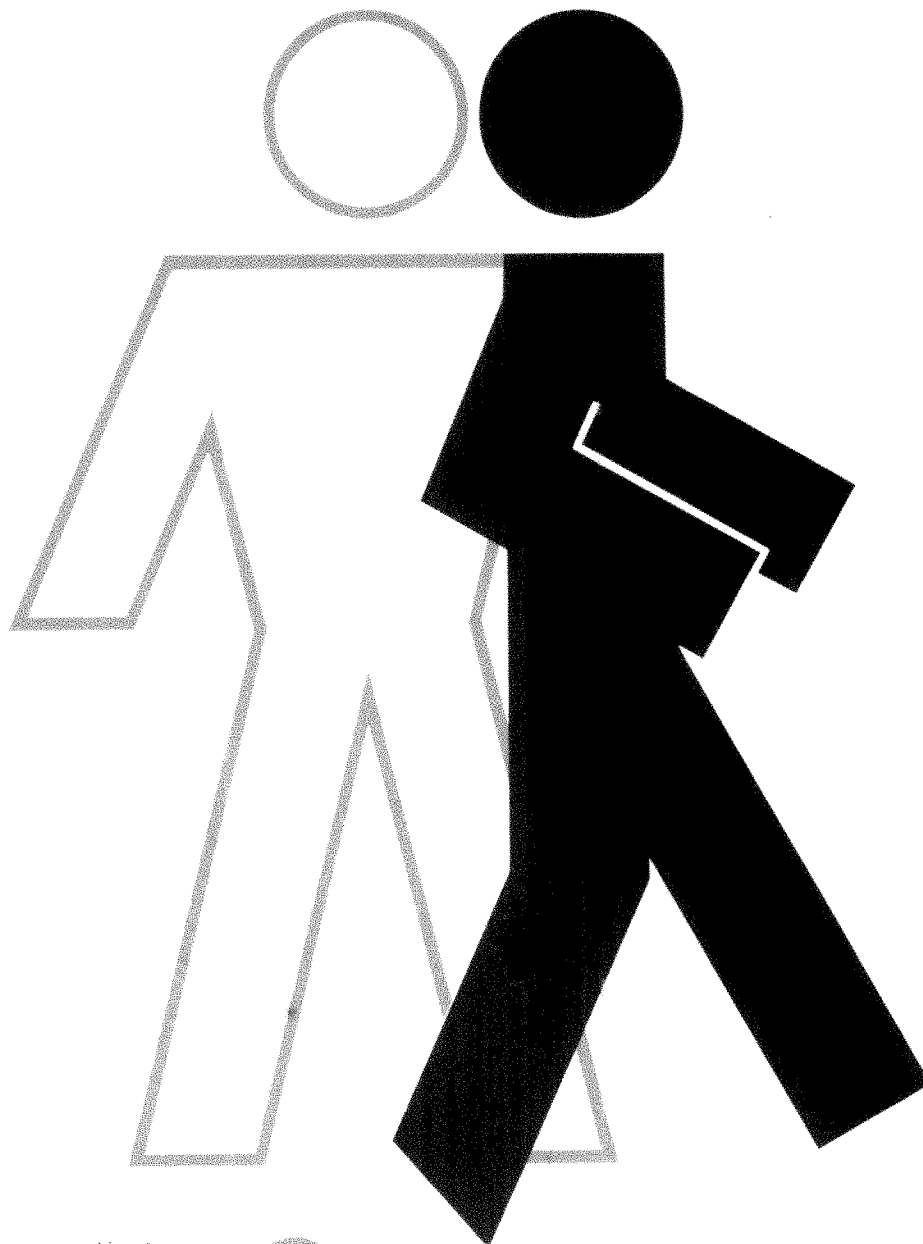
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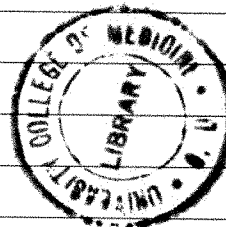
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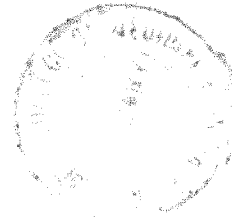
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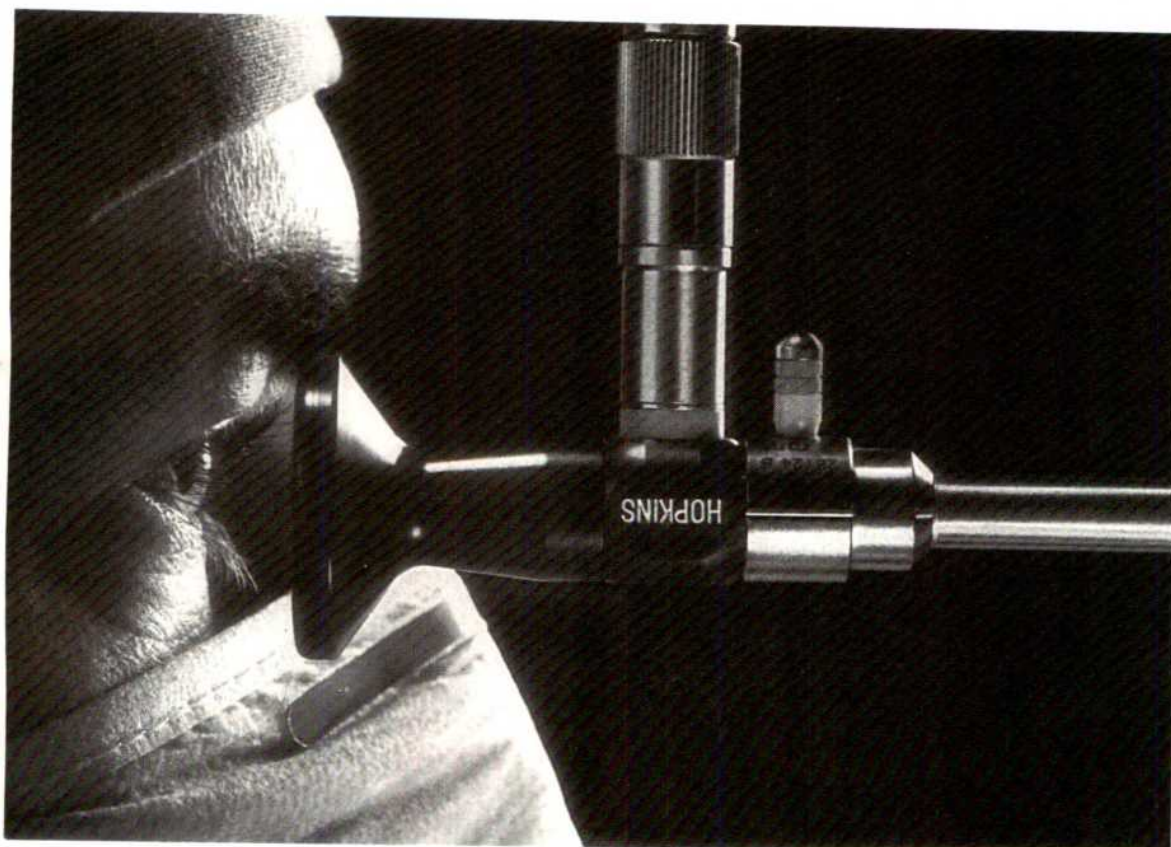
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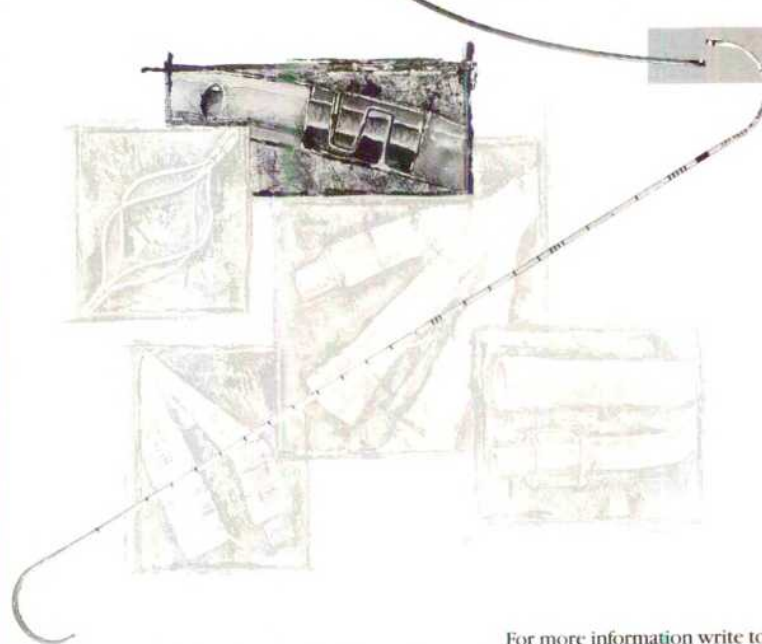
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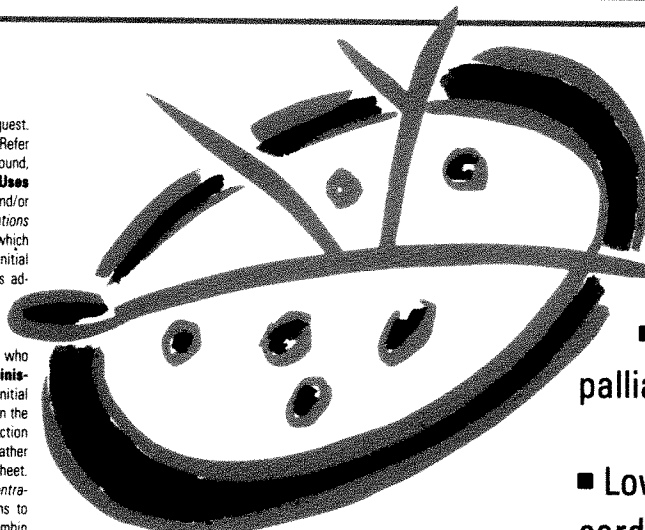
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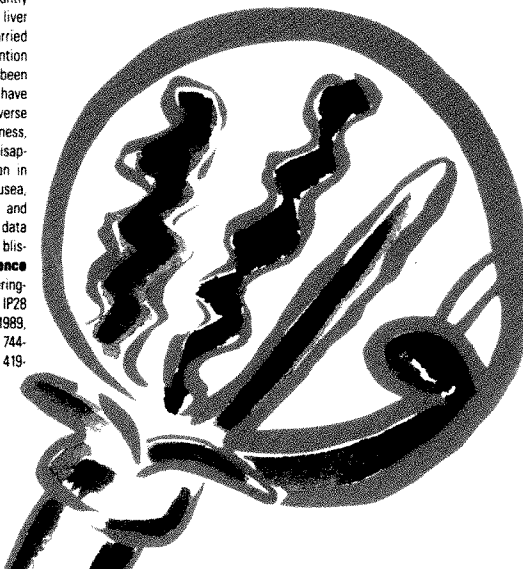
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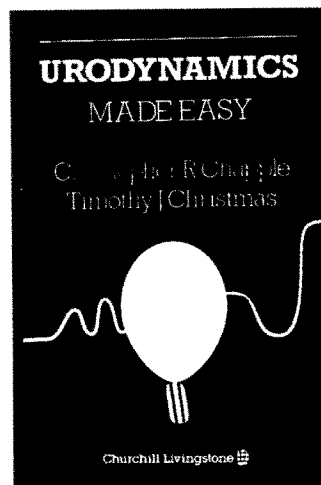
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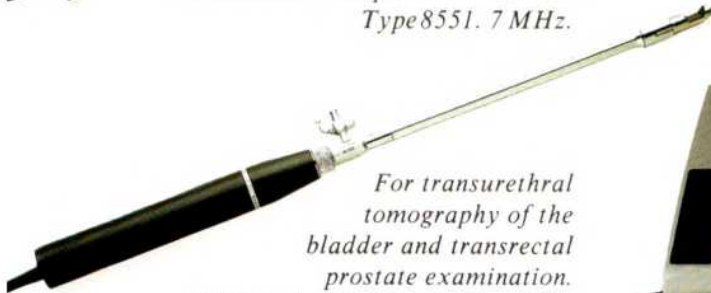
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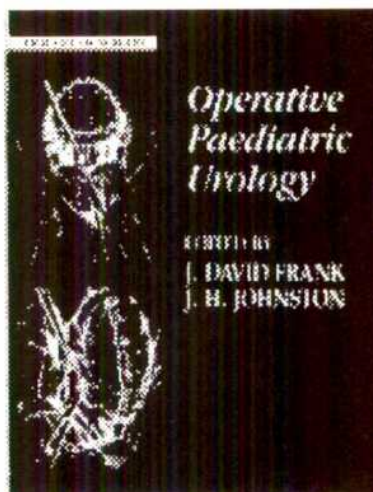
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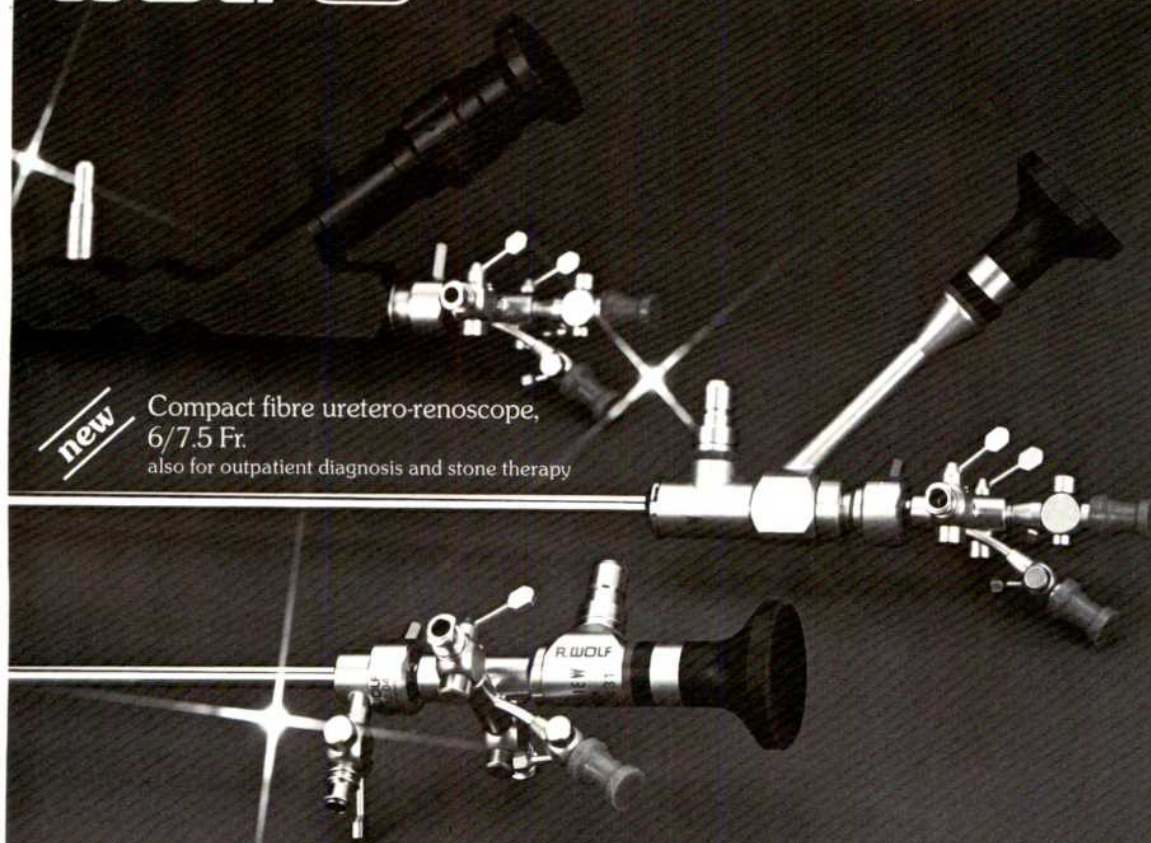


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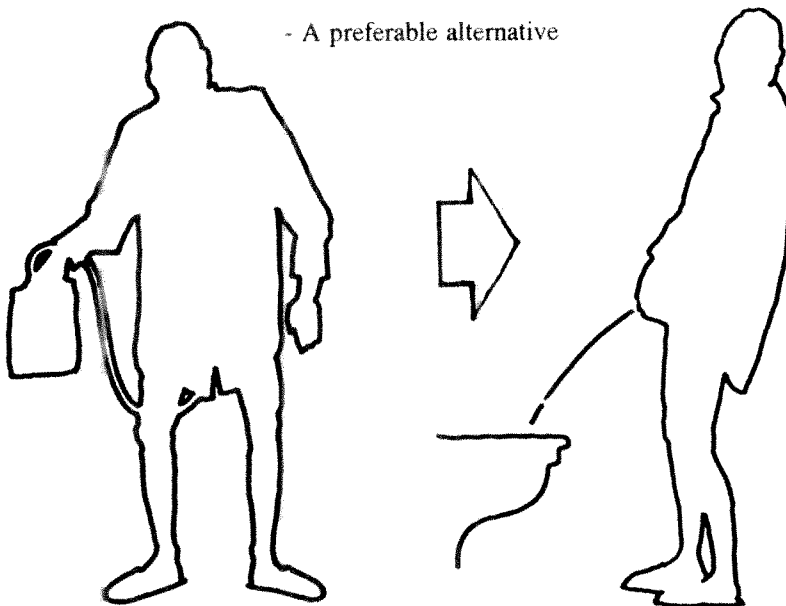


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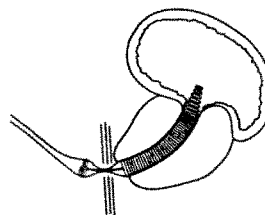
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REVIEW

Haemangioma of the Urinary Tract: Review of the Literature

H. JAHN and H. M. NISSEN

University Department of Urology, Odense Hospital, Odense, Denmark

Haemangiomas of the urinary tract are a relatively unusual entity and are seldom described in the literature. They are of clinical importance in that they are one of the benign causes of haematuria which may create problems concerning diagnosis and management.

Approximately 175 cases of renal haemangioma have been reported up to 1980 (Crissey *et al.*, 1980), 6 cases of ureteric haemangioma up to 1973 (Uhlir, 1973), 81 cases of bladder haemangioma up to 1976 (Caro and Brown, 1976) and 19 cases of urethral haemangioma up to 1983 (Roberts and Devine, 1983). Only 1 case of haemangioma located in the prostate has been reported.

A review of the literature up to the present has revealed a further 23 examples of renal haemangioma, 25 bladder haemangiomas and 1 urethral haemangioma, increasing the total number to renal haemangioma (198 cases), bladder haemangioma (106) and urethral haemangioma (20). However, haemangiomas of the urinary tract are probably more common than generally reported and we present a review of the literature on those lesions with special regard to pathology, clinical manifestations, diagnostic procedures and treatment.

General Features of Haemangiomas

Pathology

Haemangiomas are benign vascular tumours that probably arise from the embryonic rest of unipotent angioblastic cells which fail to develop into normal blood vessels. Haemangiomas can be divided into benign haemangioendotheliomas, capillary (juvenile) haemangiomas, cavernous, venous and rac-

mose (cirroid) haemangiomas. Of these vascular tumours the cavernous haemangioma is the most common histological type. The classifications quoted above are of academic interest rather than clinical relevance.

Haemangiomas occur in all parts of the urinary tract and, according to the number of cases reported, the kidney seems to be most frequently affected, followed by the bladder. Haemangiomas of the urinary tract are generally seen as isolated lesions but may also be part of congenital disorders, e.g. the Klippel-Trenaunay syndrome, Sturge-Weber syndrome and systemic angiomatosis (Esguerra *et al.*, 1973; Caro and Brown, 1976; Maeda, 1984; Campistol *et al.*, 1988).

Histologically, the lesions are composed of a mixture of endothelium-lined spaces (small, capillary; large, cavernous) containing erythrocytes and recently (or older) organised thrombi.

They grow slowly by budding, pushing into adjacent tissue where the connective tissue septa may condense to form a poorly developed capsule. They do not communicate with the surrounding vessels and therefore are not truly invasive (Peterson and Thompson, 1971).

Clinical picture

The cardinal manifestation of haemangioma in the urinary tract is haematuria. By no means all haemangiomas become clinically manifest and many are either discovered accidentally at autopsy or secondary to surgical intervention in the urinary tract.

Haematuria is often intermittent over a number of years, varying from microscopic to massive haemorrhage. Bleeding is usually spontaneous and results from thrombosis, infarction or renewed growth of the vessels following erosion of the

urinary tract epithelium. Factors such as trauma and infection prior to bleeding have been reported.

Treatment

Haemangiomas can regress spontaneously as a result of fibrosclerosis, suggesting a conservative approach wherever possible (Garcia *et al.*, 1988). Asymptomatic haemangiomas do not require treatment.

Renal Haemangioma

Pathology

Haemangiomas of the kidney are usually solitary and unilateral without predilection for side or sex. They vary in size from microscopic to 10 cm in diameter, but usually measure 1 to 2 cm. From 76 clinical and necropsy specimens of renal haemangioma it appears that the lesion occurs commonly in 3 locations—in the mucosa or subepithelial tissue of the pelvis (48.7%), in the pyramid of the kidney (42.1%) and in the cortex (9.2%), where they may cause perirenal bleeding (Weyrauch and Berger, 1951). Multiple haemangiomas in the same kidney have been found in 10 of 87 patients (12.0%) (Wallach *et al.*, 1959) and bilateral involvement has been reported twice.

Clinical picture

Haemangiomas may result in severe haematuria with or without pain. Pain is presumably caused by partial obstruction by clots or by the pressure of interstitial bleeding. Uraemia and other signs of renal failure are conspicuous by their absence. A review of 87 cases by Wallach *et al.* (1959) showed that renal haemangiomas are seldom clinically manifest before the age of 20 years, with a peak between 30 and 40 years and an equal incidence before and after the age of 40 years. The age limits range between 4 months and 78 years.

Diagnosis

Haemangioma should be suspected in any case of unilateral renal haematuria where infection, urolithiasis, malignancy, parenchymal disorders or blood dyscrasia have been excluded. The lesion is seldom diagnosed pre-operatively and, in the majority of cases, the diagnosis has resulted from pathological examination of the excised kidney.

Clinical examination and conventional radiological examinations do not usually contribute to the diagnosis. Intravenous urography and retrograde pyelography may be normal or may reveal obstruction or inconstant filling defects due to clots.

In a small percentage of cases (Hagen, 1963; Stanley *et al.*, 1975; Feczko, 1979; Mitchell *et al.*, 1982; Michel *et al.*, 1983; Yazaki *et al.*, 1985) the diagnosis and location were established by means of selective renal angiography. The difficulty in detecting these lesions by angiography is explained by their small size, the presence of thrombosed vessels and the vascular structure of the tumour (Gordon *et al.*, 1976). The angiographic findings are generally characterised by hypervascularity, but hypovascularity may also occur. Angiographic differentiation of haemangioma from renal carcinoma may be impossible but is usually based on the former's lack of mass effect, staining or pooling during the nephrogram phase and the absence of an irregular vascular encasement (Crissey *et al.*, 1980). Although angiographic techniques have improved (*e.g.* magnification angiography), a normal angiogram does not preclude the possibility of a haemangioma. For the present, angiography remains the best documented diagnostic examination.

In recent years, 9 cases have been reported in which per-operative nephroscopy established the diagnosis and/or location of the angioma in actively bleeding patients and this is a valuable guide to surgical treatment (Crissey *et al.*, 1980; Gittes and Varady, 1981; Aagaard and Hansen, 1985; Garcia *et al.*, 1988). In the light of these results, transurethral nephroscopy or per-operative nephroscopy should be considered in actively bleeding patients, especially if the angiographic findings are negative.

New techniques such as the CT scan (Schlout and Ahlen, 1987), ultrasonography (Stanley *et al.*, 1975; Schlout and Ahlen, 1987) and the technetium-99-labelled erythrocyte scan (Campistol *et al.*, 1988) are useful in establishing the distribution of the lesion. Experience in the use of these techniques is still limited and further evaluation is required.

Treatment

Haemangioma is seldom diagnosed pre-operatively and so it is impossible to recommend specific treatment. Management includes observation, nephrectomy, heminephrectomy, papillectomy and embolisation. Non-surgical management has been used in a few cases of mild haematuria and is not contraindicated in the healthy patient with mild to moderate haematuria who is otherwise clinically and radiographically well (Peterson and Thompson, 1971), provided the haemoglobin level is not falling. Most of the reported patients were managed by nephrectomy because of the extreme nature of haematuria and the difficulty in distinguishing the

lesion from diseases requiring nephrectomy, such as carcinoma. Partial nephrectomy is recommended by many authors and has been successfully employed in several cases of minor haemangioma (Hagen, 1963; Feczko, 1979; Crissey *et al.*, 1980; Gittes and Varady, 1981; Mitchell *et al.*, 1982; Michel *et al.*, 1983; Aagaard and Hansen, 1985). Conservative surgical treatment should be considered when the lesion is small and the condition can be diagnosed with any degree of certainty. The incidence of multiple lesions in the affected kidney is not a strong deterrent to this management. Otherwise, nephrectomy may be justified on the basis that it is usually difficult to identify a haemangioma, that the differential diagnosis includes malignancy, that 12% of lesions are multiple and that nephrectomy may be performed as a life-saving emergency procedure following severe bleeding.

Ureteric Haemangioma

Pathology

Haemangiomas occur as sessile or pedunculated tumours and range in size from a few mm to $6.5 \times 0.5 \times 0.3$ cm. In 1 patient the specimen included 3 tumours. In 5 patients the tumours were located in the lower third of the ureter, often prolapsing through the ureteric orifice.

Clinical picture

Haematuria and/or ureteric pain.

Diagnosis

Haemangioma is usually revealed by intravenous urography and retrograde pyelography as a non-specific filling defect. Cystoscopic biopsy without significant bleeding was performed in 1 case (Brodny and Hershman, 1954). The remaining cases were diagnosed post-operatively by pathological examination. Ureteroscopy can be a useful diagnostic examination.

Treatment

Nephroureterectomy has been performed twice because the exact nature of the tumour was unknown. Ureterotomy has been performed successfully in 1 patient (Brodny and Hershman, 1954) through an incision well outside the origin of a pedunculated haemangioma. In 1 case where 3 haemangiomas were located in the lower third of the ureter, the affected ureter was resected and replaced by a small intestinal loop (Uhler, 1973). When a haemangioma is suspected, a conservative operation is recommended.

Bladder Haemangioma

Pathology

Haemangioma has been recorded in 6 of 954 benign bladder tumours (0.6%) (Melicow, 1955). Haemangioma of the bladder varies from a few mm to 10 cm in diameter. In most cases the tumours measure 1 to 2 cm and they are usually sessile, with a smooth or irregular surface.

An analysis of 31 cases (Hendry and Vinnicombe, 1971) revealed that 21 tumours (66%) were solitary and generally involved the upper half of the bladder. Involvement of the trigone, ureteric orifice and bladder neck was exceptional. In 36% of cases the lesion appeared to be fairly superficial, involving only the submucosa, while in the remaining 64% the muscle layers were affected. In many cases the tumour showed the characteristics of an iceberg, having considerable extravascular extension. In 31% of cases concomitant haemangioma of the skin and external genitalia was reported.

A review of an additional 16 cases of bladder haemangioma revealed that the muscle layers were involved in 9 cases (56%) and in 5 cases (32%) extravascular extension was reported.

Clinical picture

Haemangiomas are usually associated with recurrent isolated haematuria. Other symptoms include suprapubic pain, vesical irritation and urinary retention, especially if the lesion is located at the bladder neck. Renal colic may also be present if the ureteric orifice is occluded. A review of 21 patients (Fuleihan and Cordonnier, 1969) revealed that the lesions were clinically manifest from the age of 1 to 60 years; 62% of the patients were less than 15 years old and 28.5% were over 50 years of age.

Diagnosis

Haemangioma is confirmed by cystoscopy, with the typical finding of a purple, multilobulated and sessile tumour that must be differentiated from bladder endometriosis, melanoma or sarcoma. The presence of haemangioma elsewhere in the skin and external genitalia should be highly suggestive of the diagnosis. When haemangioma is suspected, endoscopic biopsy should be avoided as it could precipitate an uncontrollable haemorrhage since only a small part of the lesion may appear on the surface. The intravenous urogram may be unremarkable, or may reveal intravesical filling defects dependent on the size and localisation of the tumour, and sometimes it may even be calcified.

Accurate staging of the tumour is difficult but is advisable in order to select an appropriate form of

treatment, avoiding the risks of transurethral resection. Bimanual palpation, even under anaesthesia, may not be helpful in assessing the true dimensions of the tumour because of its soft consistency. Pelvic arteriography (Esguerra *et al.*, 1973), technetium-99-albumin scan (Bryniak *et al.*, 1979) and ultrasonography (Gupta and Bhargava, 1987) have proved valuable in staging the tumour, but experience of these examinations is limited and further case studies are needed. A negative pelvic angiogram or scan does not preclude further extension of the lesion than is revealed by cystoscopy. The low echogenic structure of haemangiomas makes the use of transabdominal ultrasonography of little use in staging. Although not reported, intravesical and transrectal/vaginal ultrasonography could improve the staging results.

Treatment

Haemangiomas have been managed by observation, transurethral resection and electrocoagulation, the injection of sclerosing agents, radiation, various degrees of bladder resection (including total cystectomy) and laser treatment. Small superficial lesions have been successfully removed transurethrally (Fuleihan and Cordonnier, 1969; Hendry and Vinnicombe, 1971; Susset *et al.*, 1981) but in view of the varied histological picture, transurethral resection and electrocoagulation might be hazardous because they might precipitate a massive haemorrhage; furthermore, they do not ensure entire extirpation of the lesion and so may lead to local recurrence.

Either partial cystectomy or local excision appears to be the most effective and the safest method of treatment and is frequently recommended as the treatment of choice (Hendry and Vinnicombe, 1971; Esguerra *et al.*, 1973; Caro and Brown, 1976; Proca, 1977) regardless of where the lesion is located in the bladder. Fortunately, the tumour is most commonly seen away from the trigone and bladder outlet, which makes surgery safe and relatively simple. Otherwise, conservative treatment and transurethral management are advocated in cases where the trigone, ureteric orifices and bladder neck are affected (Fuleihan and Cordonnier, 1969). Nevertheless, endoscopic treatment should not be carried out unless the patient is prepared for open surgery.

Although 2 patients were cured by radiotherapy (Fuleihan and Cordonnier, 1969), such treatment is not felt to be acceptable for these benign lesions. In a recent study, neodymium: YAG laser energy was delivered endoscopically to 13 cases of haeman-

gioma (Smith, 1990). The results seem promising and this treatment should be considered as an alternative in cases where surgical risk precludes surgery or where the haemangioma involves most of the bladder. Further information concerning laser treatment would be desirable in order to support its practicability. Whatever kind of treatment one may prefer, follow-up cystoscopic examinations are mandatory.

Urethral Haemangioma

Pathology

These haemangiomas are either papillary or sessile and occur as single or multiple lesions. As with haemangiomas of the bladder, they often extend further than is grossly evident (Manuel *et al.*, 1977).

Clinical picture

They may cause isolated haematuria or bloody urethral discharge.

Diagnosis

Haemangiomas are diagnosed by cystoscopy and, as with haemangiomas of the bladder, cutaneous haemangiomas elsewhere in the skin should provide a clue.

Treatment

The tumours are managed by local resection, electrocoagulation and by excision of a minor or wider part of the urethra. Endoscopic management is recommended for small, isolated lesions (Manuel *et al.*, 1977; Roberts and Devine, 1983) but the possibility of local recurrence should be borne in mind since even small lesions may extend further than is immediately obvious. In the case of more extensive lesions, or recurrence after endoscopic management, open exploration with resection of the involved tissue is advised followed by appropriate urethral reconstruction (Manuel *et al.*, 1977; Roberts and Devine, 1983; Maeda, 1984). The borders of the excised tissue should be marked and, if there is histological evidence of extension beyond the excised border, further surgical treatment should be instituted immediately (Manuel *et al.*, 1977).

Summary

General features

Haemangiomas are benign vascular tumours. They can regress spontaneously as a result of fibrosclerosis, suggesting a conservative approach wherever possible. Asymptomatic haemangiomas do not require treatment.

Renal haemangioma. In all, 198 cases have been reported. The lesion is usually solitary and unilateral and occurs most often in the pyramid, and in the mucosa or subepithelial tissue of the pelvis. In some cases a tentative diagnosis of haemangioma has been made by means of selective renal angiography and pre- or per-operative renoscopy. Partial nephrectomy is recommended in cases of minor haemangioma.

Ureteric haemangioma. Six cases have been described. When haemangioma is suspected a conservative operation is recommended.

Bladder haemangioma. A total of 106 cases have been reported. Many of the tumours had the characteristics of an iceberg, with considerable extravascular extension making endoscopic management less suitable because of the possibility of massive haemorrhage or recurrence. Consequently, many authors prefer local excision. In the case of endoscopic treatment the patient should be prepared for open surgery.

Urethral haemangioma. Twenty cases have been described. The lesions often extend further than is immediately apparent. Endoscopic management is recommended for small lesions and, in the case of more extensive lesions, open exploration is advised followed by appropriate urethral reconstruction.

N.B. This review is based on an extensive review of the literature and not all references are included in the bibliography. A complete list may be obtained from the authors.

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Disturbance in Sodium Regulating Hormones in Chronic Obstructive Uropathy

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Summary—Serum atrial natriuretic peptide (ANP), plasma renin activity (PRA), angiotensin II (All) and aldosterone levels have been studied in patients with chronic bilateral ureteric obstruction resulting from high pressure chronic retention of urine (HPCR), both in the obstructed state and during the post-obstructed period. Increased ANP levels observed during chronic obstruction fell rapidly following urinary tract decompression by urethral catheterisation. Serum ANP resurged briefly within 24 h but stabilised thereafter at a lower level. PRA was initially suppressed but rose after catheterisation, the increase lagging behind the changes seen for ANP. Rising levels of All and aldosterone followed this trend but, unlike PRA, levels were not completely suppressed in the obstructed state. The observed hormonal changes probably reflect homeostatic mechanisms directed to the maintenance of sodium and water balance during obstruction and to limitation of the diuresis following its relief.

The disturbance in renal function which results from chronic bilateral ureteric obstruction (BUO) is characterised by glomerular and tubular dysfunction, frequently leading to impaired sodium and water excretion, circulatory volume overload and hypertension (Jones *et al.*, 1987a). Following relief of obstruction, changes in diuresis and natriuresis (Bishop, 1985; O'Reilly *et al.*, 1986; Jones *et al.*, 1987a), consequent upon improvement in glomerular filtration rate (GFR) and renal tubular function (Jones *et al.*, 1988) have been well documented both in animals and in man (Vaughan and Gillenwater, 1973; Jones *et al.*, 1987b); however, the concurrent flux in sodium regulating hormones which might accompany such changes has not been adequately studied in the human.

This report therefore examines alterations in atrial natriuretic peptide, plasma renin, angiotensin II and aldosterone in patients with BUO due to high pressure chronic retention of urine studied in the obstructed state, after relief of

obstruction and subsequently during the post-obstructive diuresis.

Patients and Methods

Five patients (mean age 69 years, range 58–73) with typical features of high pressure chronic retention (George *et al.*, 1983) were studied. None had a past history of urinary tract infection and mid-stream urines were sterile and cell-free at the time of investigation. No patient had ever received medication with effects on cardiovascular or renal function and all other drugs were avoided during the study. The 5 men were selected from a cohort of 14 patients presenting with HPCR over a 15-month period. The remaining 9 patients were deemed unsuitable for study due to intake of drugs with cardiac and/or renal effects at the time of admission (7 patients) or to the presence of urinary tract infection (2 patients). Measurements were performed in hospital over 5 days, during which time the patients received a normal diet and fluids were taken *ad libitum*. Intravenous infusions were not administered at any time.

Before each assessment patients remained recumbent overnight and were instructed to remain

supine until venesection at 08.00; thereafter patients were ambulant throughout the day, venesection being repeated in the erect posture at 08.30. Blood was drawn for measurement of ANP, renin, angiotensin II and aldosterone. All specimens were immediately separated at 4°C and stored at -70°C prior to assay.

Baseline measurements were taken in the obstructed state. The following day obstruction was relieved at 08.30 by urethral catheterisation and erect ANP, PRA, AII and aldosterone were measured 2, 4 and 8 h thereafter. Supine and erect morning measurements were continued in the post-obstructed period (as for baseline studies) at 24, 48 and 72 h following catheterisation.

Consecutive 24-h urine collections were commenced prior to bladder drainage and continued during the study period for measurement of daily urine volume and electrolyte excretion. Serum biochemistry, body weight and supine and erect blood pressure were monitored daily; plasma volume was determined at the beginning and end of the study using an iron dilution technique (MacKenzie and Tindle, 1959).

Statistical analysis was by analysis of variance of log_e transformed data (ANP) and of simple mean values (PRA, AII and aldosterone).

Results

All patients had a typical post-obstructive diuresis and natriuresis and plasma volume fell in 4 of the 5 men over the period of study (Table).

Erect ANP levels fell rapidly following catheterisation ($P < 0.0001$ at 8 h), increased marginally by 24 h and remained at lower levels 72 h later. Concurrent erect PRA was initially low but rose significantly by 48 h ($P < 0.0001$). Erect AII levels were normal or elevated in the obstructed state and rose significantly during the study ($P < 0.001$ at 48 h). Prior to drainage, erect aldosterone was within the normal range in all patients but subsequently levels rose in 3 and were markedly elevated in 2 patients at the end of the study (Fig.). The persistently high levels of aldosterone occurred in those patients with the greatest degree of renal impairment at the outset.

Supine hormonal changes mirrored the erect pattern throughout but ANP levels were significantly higher than in the erect state (mean supine ANP: 172 pg/ml, erect 129 pg/ml: $P < 0.001$). This postural difference was lost following bladder drainage. Conversely, there was no postural effect on PRA before catheterisation but differences emerged 48 h later (mean supine 3.8 ng/ml/h, erect 8.9 ng/ml/h: $P < 0.005$). AII was significantly higher erect than supine throughout ($P < 0.005$).

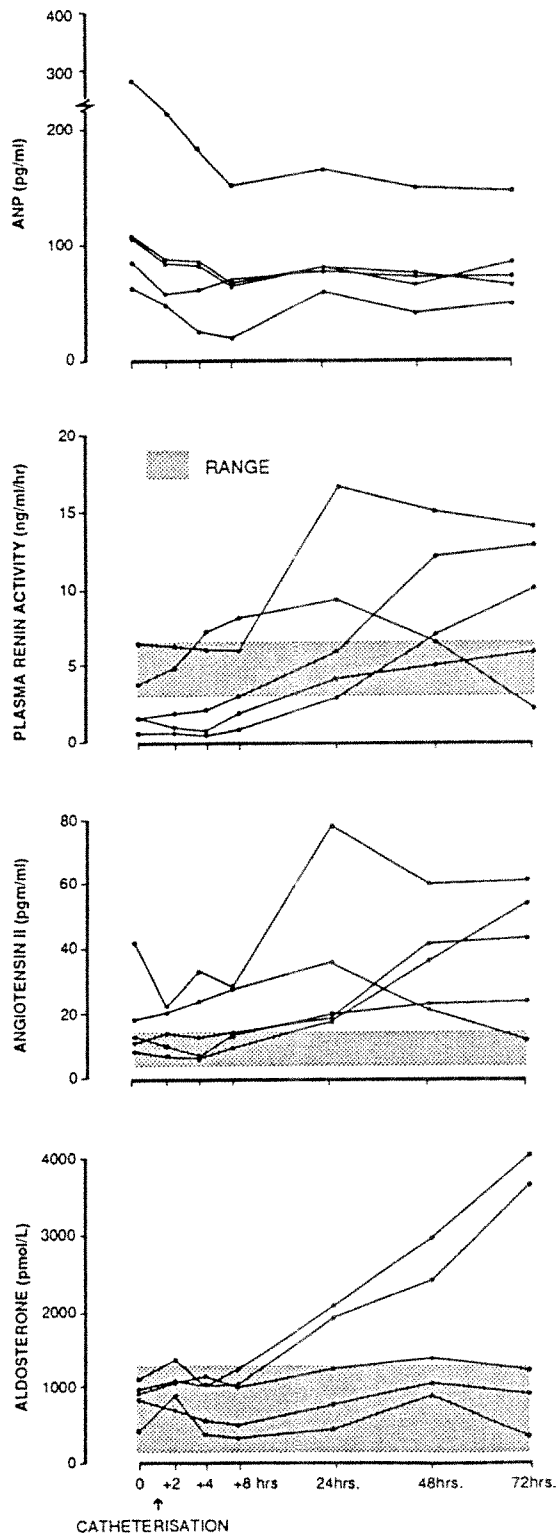
Discussion

HPCR is recognised as an ideal stable clinical model by which to study the effects of chronic bilateral ureteric obstruction (Jones *et al.*, 1987a and b); nevertheless, only 5 patients (of 14 screened) matched stringent exclusion criteria which ensured that infection, medicines with cardiovascular or

Table Results

	<i>Obstructed (pre-catheter)</i>	<i>0-24 h</i>	<i>24-48 h</i>	<i>48-72 h</i>	<i>72-96 h</i>
Urine volume (ml)	1730 ± 662	3348 ± 670	2232 ± 673	2282 ± 720	2404 ± 696
U _{Na} V (mmol)	109 ± 23	300 ± 11	149 ± 20	122 ± 24	106 ± 15
Plasma volume (ml/kg)	47.5 ± 7.2				43 ± 9.4
Supine BP systolic	158 (148-165)	155 (150-165)	140 (130-148)	126 (115-135)	124 (115-135)
Supine BP diastolic	90 (75-100)	95 (75-100)	81 (65-95)	68 (60-75)	65 (60-70)
Erect systolic	148 (130-160)	155 (130-160)	128 (120-155)	120 (90-145)	119 (95-140)
Erect diastolic	99 (85-110)	90 (85-110)	82 (65-95)	74 (60-90)	73 (60-80)
Weight (kg)		66.4 (48-86)	63.7 (47.3-82.5)	63.5 (47.3-83)	63.3 (47.3-82.5)
Serum creatinine (mmols/L)	0.25 (0.09-0.53)	0.23 (0.51-0.08)	0.23 (0.51-0.08)	0.23 (0.52-0.08)	0.22 (0.49-0.08)

Figures with parentheses denote mean values and range. Those without denote mean values and 95% confidence limits. Urinary volume and sodium excretion (U_{Na}V) were greatest in the 24 h following catheterisation. Significant decreases were recorded over the study period for erect and supine diastolic BP ($P = 0.008$ and $P < 0.0001$) and erect systolic BP ($P < 0.0001$). Mean patient weight also fell significantly with time ($P = 0.0009$).



renovascular actions and intravenous fluid replacement did not obscure the subtle hormonal changes which might be expected after relief of chronic obstructive uropathy.

ANP was high in the obstructed state in all patients and although there is debate as to the true "normal" in this age group (Ohashi *et al.*, 1987), the observed levels were raised by comparison with other reported ranges (Anderson and Bloom, 1986; Espiner and Richards, 1989). BUO is known to induce fluid retention due to glomerular and renal tubular dysfunction (Jones *et al.*, 1988) and the increase in atrial natriuretic peptide is therefore likely to represent a response to circulatory volume overload; similar observations have been made in other conditions characterised by increased intravascular volume (Fonseca *et al.*, 1985; Burnett *et al.*, 1986). Since ANP exerts some of its effects by decreasing medullary hypertonicity (thereby enhancing natriuresis (Atlas and Maack, 1987)), this may be a mechanism by which both sodium and water excretion are maintained in this condition despite a decreased GFR (Jones *et al.*, 1987a and b); similarly, the presence of oedema may be explained by ANP-mediated fluid shift from the intravascular to the extravascular space (Goetz, 1988).

The low PRA observed during obstruction reflects the prevailing sodium and water overload and possibly inhibition by high circulating levels of ANP (Cuneo *et al.*, 1987). However, suppression of AII and aldosterone levels was less convincing, with levels remaining within or above the normal range. BUO disturbs renal blood flow (Wright, 1982) and local generation of AII, a mechanism by which GFR may be altered under these circumstances (Kastner *et al.*, 1984), might explain this relative imbalance in PRA and AII levels.

Following catheterisation the rate of fall in erect ANP was rapid and the magnitude of change greater than that seen for normal diurnal variation (Richards *et al.*, 1987). This change was accompanied by an immediate diuresis and natriuresis, an effect demonstrated after relief of acute obstruction in animals (Purkeson *et al.*, 1989). The resurgence in erect ANP levels between 8 and 24 h after catheterisation was a constant and interesting finding. The sharp initial reduction in ANP may facilitate fluid transfer back to the intravascular

Fig. Serial plasma concentrations of atrial natriuretic peptide (ANP), plasma renin activity, angiotensin II and aldosterone before and after relief of bilateral chronic obstructive uropathy. Stippled area denotes the normal laboratory range.

compartment from the interstitium (Goetz, 1988), resulting in a temporary rise in vascular volume which in turn triggers a secondary rise in ANP. These observations support the hypothesis that ANP-mediated interstitial fluid transfer may be a primary mechanism of intravascular volume control; the natriuretic properties of the peptide constitute a final but relatively delayed mechanism of volume homeostasis. Drainage also abolished the postural difference in ANP and was associated with the emergence of a postural rise in PRA. These changes probably reflect the fall in plasma volume as measured before and after study.

During the period following relief of obstruction, trends in hormone flux were appropriate to limiting the natriuresis and diuresis. Significant changes in aldosterone levels were, however, restricted to those patients with the greatest degree of renal impairment. The progressive and continued elevation in sodium retaining hormones following catheterisation in this study provides strong evidence that PRA, AII and aldosterone play a significant role in arresting the sodium and water loss which follows relief of BUO.

It is concluded that during BUO there is a significant disturbance in the endocrine mechanisms controlling sodium and water balance which, in the post-obstructed period, undergo major flux directed towards restoration of normal homeostasis. Such changes may play a part in controlling the disturbed equilibrium induced by BUO and they are probably important in limiting the post-obstructive diuresis.

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Staghorn Calculi—Long-term Results of Management

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Summary—We have treated 167 patients with staghorn calculi. Conservative therapy was used in 61 patients who have been followed up for 1 to 18 years (average 7.8). Chronic renal failure occurred in 22 of these patients and 7 died from uraemia. The causes of chronic renal failure were bilateral staghorn calculi, staghorn calculi and contralateral urinary calculi, and chronic pyelonephritis of the contralateral kidney. The morbidity and mortality rates following conservative treatment were higher than those following surgical management. The pathological findings in 47 kidneys after nephrectomy showed severe hydronephrosis, renal abscess and xanthogranulomatous pyelonephritis. These results indicated that staghorn calculi destroyed the kidney and early complete removal of these stones is advisable.

The management of staghorn calculi has given rise to controversy. Libertino *et al.* (1971) analysed 17 cases of staghorn calculi in solitary kidneys and concluded that medical therapy was the treatment of choice for asymptomatic calculi. Others have stated that non-surgical management led to deterioration in the kidney, and suggested that surgical management was preferable (Blandy and Singh, 1976; Vargas *et al.*, 1982). Recently, surgical management has achieved dominance as the development of surgical techniques progresses (Gil-Vernet, 1965; Smith and Boyce, 1968). However, complete removal of staghorn calculi is often difficult and the incidence of residual stone fragments is as high as 25% (Singh *et al.*, 1975; Rous and Turner, 1977). Surgical management may also cause vascular damage to the kidney and a decrease in renal function.

We have reviewed patients with staghorn calculi and examined the pathological findings in excised kidneys, in order to investigate complications and to improve the management of staghorn calculi.

Patients and Methods

Between April 1965 and March 1984, 167 patients with staghorn calculi (191 kidneys) were seen at

this hospital. The patients ranged in age from 17 to 84 years (average 51.0) and included 97 females and 70 males; female patients thus predominated 1.4:1.0. A staghorn calculus was defined as one that fills the renal pelvis and extends into at least 2 major caliceal systems. The staghorn calculi were unilateral in 143 patients (right-sided in 70 and left-sided in 73) and bilateral in 24. Four patients had solitary kidneys. Chronic renal failure was diagnosed when the creatinine level exceeded 2.0 mg/dl.

Management consisted of conservative therapy without surgery in 71 patients (87 kidneys), nephrectomy in 47 (47), extended pyelolithotomy in 33 (33), nephrolithotomy in 18 (18) and partial nephrectomy in 6 (6) (Table 1). Of 71 patients receiving conservative treatment, 61 have been followed up for 1 to 18 years (average 7.8). Four of 71 patients

Table 1 Management of Staghorn Calculi in 191 Kidneys (167 patients)

	No. of kidneys (%)	
Conservative therapy without surgical treatment	87	(45.6)
Nephrectomy	47	(24.6)
Extended pyelolithotomy	33	(17.3)
Nephrolithotomy	18	(9.4)
Partial nephrectomy	6	(3.1)

presented with chronic renal failure and 16 had bilateral staghorn calculi. Of the 47 patients treated by nephrectomy, 38 have been followed up for 2 to 18 years (average 10.8). Nephrectomy was performed in patients with severe renal damage and infection, and the pathological findings were assessed. Of 18 patients undergoing nephrolithotomy, 17 were followed up for 1 to 12 years (average 4.4). Of 33 patients undergoing extended pyelolithotomy, 27 have been followed up for 2 to 12 years (average 5.2). Six patients with partial nephrectomies were followed up for 2 to 11 years (average 5.6). In 8 patients with bilateral staghorn calculi, treatment varied for each kidney.

Results

Of 167 patients, 13 (7.8%) were asymptomatic and 154 (92.2%) presented with symptoms (Table 2). The most common symptom was flank or abdominal pain. Urine cultures were performed in 78 patients (Table 3). Organisms grew in 85% the most frequent organism being *Proteus mirabilis*. In 4 of 6 asymptomatic patients, urine culture showed urinary infection to be present. Septic shock occurred in 2 patients with urinary obstruction and pyelonephritis. Chronic renal failure occurred in 15 of 24 patients (63%) with bilateral staghorn calculi.

Conservative therapy

The results of conservative therapy are summarised in Table 4. Of 61 patients followed up, 39 (64%) had unilateral staghorn calculi with a normal

Table 2 Symptoms of Staghorn Calculi in 167 Patients

Symptoms	No. of patients (%)
Pain	115 (68.9)
Fever	43 (25.7)
Gross haematuria	30 (18.0)
Asymptomatic	13 (7.8)

Table 3 Urine Cultures in 78 Patients with Staghorn Calculi

Organisms	No. (%)
<i>Proteus</i> species	27 (34.6)
<i>E. coli</i>	11 (14.1)
<i>Klebsiella</i>	9 (11.5)
<i>Staph. species</i>	8 (10.3)
<i>Pseudomonas</i>	7 (9.0)
Others	4 (5.1)
No growth	12 (15.4)

Table 4 Results of Conservative Therapy in 61 Patients

	No. of patients (%)
Normal renal function	39 (63.9)
Chronic renal failure	
Bilateral staghorn calculi	13 (21.3)
Contralateral urinary calculi	8 (13.1)
Chronic pyelonephritis of contralateral kidney	1 (1.6)

Death due to uraemia (7) and other causes (3).

contralateral kidney and normal renal function. Chronic renal failure occurred in 22 patients (36%). In 19 of 22 patients chronic renal failure developed during follow-up. The causes were bilateral staghorn calculi (13), staghorn calculi and contralateral urinary calculi (8) and chronic pyelonephritis of the contralateral kidney (1). Seven of 61 patients (12%) died of uraemia due to bilateral staghorn calculi (4) and contralateral urinary calculi (3). Three patients died from other causes.

Nephrectomy

Of 38 patients followed up, 30 (79%) had normal renal function. Chronic renal failure occurred during follow-up in 8 patients (21%). The causes were staghorn calculi or renal calculi in the remaining kidney (5) and chronic pyelonephritis (3). Two patients (5%) died from uraemia due to renal calculi with chronic pyelonephritis in the remaining kidney. Two patients died from other causes. The pathological findings in 47 kidneys after nephrectomy showed chronic pyelonephritis in 47 and severe hydronephrosis in 31 (Table 5). Chronic pyelonephritis was seen in all excised kidneys and acute pyelonephritis or abscess was often combined with chronic pyelonephritis.

Extended pyelolithotomy

Of 27 patients followed up, 24 (89%) had normal renal function and 3 had chronic renal failure. One patient died from uraemia due to chronic pyelo-

Table 5 Pathological Findings in 47 Kidneys after Nephrectomy (47 patients)

Pathological findings	No. of kidneys (%)
Chronic pyelonephritis	47 (100.0)
Hydronephrosis	31 (66.0)
Acute pyelonephritis	13 (27.7)
Abscess formation	8 (17.0)
Xanthogranulomatous pyelonephritis	1 (2.1)

nephritis caused by bilateral recurrent urolithiasis. Residual calculi were found in 6 patients (22%).

Nephrolithotomy

Of 17 patients followed up, 16 (94%) had normal renal function. One patient with bilateral staghorn calculi developed chronic renal failure after a right nephrolithotomy. It was not possible to remove calculi completely in 1 patient. No patient died from uraemia.

Partial nephrectomy

Four of 6 patients had normal renal function. Two patients developed chronic renal failure after operation; 1 had a solitary kidney and the other had bilateral staghorn calculi which were treated with left partial nephrectomy and right extended pyelolithotomy.

Discussion

Singh *et al.* (1973) and Vargas *et al.* (1982) reported that asymptomatic staghorn calculi were rare and the concept of the silent staghorn calculus was incorrect. Our findings confirm that asymptomatic patients were few in number. Asymptomatic patients often have positive urine cultures and the silent staghorn calculi may give rise to symptoms sooner or later.

Blandy and Singh (1976) studied 40 patients with staghorn calculi treated conservatively and the mortality rate was 28% compared with 7.2% in patients treated surgically. Rous and Turner (1977) claimed that the mortality rate following conservative therapy was 30%. Although our mortality rate is considerably lower (11.5%), it still exceeds that of extended pyelolithotomy or nephrolithotomy. It is difficult, however, to make a straightforward comparison as the conservative group contained patients in generally poor health. The morbidity and mortality rates were particularly high in patients with bilateral staghorn calculi and we have therefore concluded that surgical management is preferable.

The pathological findings in kidneys following nephrectomy showed that the deterioration of kidneys with staghorn calculi was caused by

infection and obstruction. Infection was seen in every case and obstruction exacerbated infection and deterioration. These results also suggest that infection and obstruction can become life-threatening and that the morbidity and mortality rates are much higher with conservative treatment.

Complete surgical removal of staghorn calculi should be performed if the patient's general condition and age allow. However, it is often difficult to remove the stones completely and residual and recurrent calculi present serious problems. Since urinary tract infection and metabolic abnormalities are important factors in the pathogenesis of staghorn calculi, we must evaluate underlying diseases. Long-term success in the management of staghorn calculi depends on complete removal of the calculi and a decrease in the recurrence rate.

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Recurrent Kidney Stones: Causes and Diagnostic Criteria in Patients from Campania (Southern Italy)

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Summary—A study was carried out on 180 recurrent kidney stone formers from the Campania region of southern Italy. The data showed that this hypercalciuric population was similar to that in previous studies; however, there was no difference in terms of parathyroid activity when compared with normal controls. The slightly depressed serum levels of vitamin D in hypercalciurics indicate that gut calcium absorption is not directly related to vitamin D levels. We found no difference in the prevalence of metabolic abnormalities associated with stone formation between the patients in this series and those in previous studies.

Several metabolic disorders have been described in nephrolithiasis, including hypercalciuria, hyperuricosuria and hyperoxaluria, and the detection of these disorders may have practical applications in the treatment of specific metabolic defects (Pak *et al.*, 1981). Various protocols have been suggested for ambulatory or in-patient evaluation (Coe and Kavalach, 1974; Rose, 1976; Pak *et al.*, 1980).

We present data from an ambulatory study of patients with recurrent kidney stones, all of whom were born and reside in the Campania region of southern Italy. The classification criteria of Pak *et al.* (1980) were used with 2 variations: (1) patients were evaluated on a standardised diet instead of an undefined low calcium diet; (2) the oral calcium loading test was not performed in hypercalciurics for reasons discussed below.

Patients were divided into 12 subgroups: type I and type II absorptive hypercalciuria, renal hypercalciuria, type I renal tubular acidosis, primary hyperparathyroidism, calcium urolithiasis with hyperuricosuria, enteric hyperoxaluria, primary hyperoxaluria, uric acid lithiasis, infection lithiasis, cystine lithiasis and no metabolic abnormality.

Patients and Methods

Between March 1983 and June 1986 we studied 180 recurrent stone forming patients comprising 99 men and 81 women (age range 10–67 years) and 26 normal control subjects (15 men and 11 women aged from 12 to 62 years). None had received any treatment affecting calcium, uric acid or oxalate metabolism, such as vitamin D, aspirin, ascorbic acid or acetazolamide; 24-h urine specimens were collected on days 3 and 4 of a 4-day 1000 mg calcium diet, and on days 6 and 7 of a 7-day 400 mg calcium diet comprising 100 mEq sodium, 900 mg phosphorus, 300 mg carbohydrates and 70 g protein (total 2100 calories). A 600 mg calcium supplement (Calcium Sandoz tablets) was added to the low calcium diet to achieve the 1000 mg diet. All urine collections were tested for calcium, phosphorus, creatinine, uric and oxalic acid and, during the low calcium diet, for cyclic adenosine monophosphate (AMP). At the end of the low calcium diet, and after a 12-h fast, 2-hourly timed urine samples were collected between 0900 and 1100 h and tested for calcium, phosphorus, creatinine and cyclic AMP. At 1000 h blood samples were taken for calcium, ionised calcium, phosphorus, creatinine, parathormone (PTH) and cyclic AMP. In addition, 74 patients with hypercalciuria, 10 with no metabolic disorder and 55 normal controls were tested

for 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$) serum levels. Calcium was assayed using an atomic absorption spectrophotometer (Unicam), ionised calcium using a specific electrode (Orion SS20), phosphorus, creatinine and uric acid by autoanalyser, and oxalic acid using an enzymatic method (Sigma kit). Serum parathormone was assayed by radioimmunoassay (RIA) using an antiserum which recognised the carboxyterminal fragment of the PTH molecule (Arnaud *et al.*, 1974); the intra-assay and inter-assay coefficient of variation was 5.6 and 6.6% respectively. Cyclic AMP was estimated by RIA directly from acidified and diluted urine, according to Steiner *et al.* (1972), and also from EDTA-plasma following acetylation according to Harper and Brookers (1975); the inter-assay and intra-assay coefficient of variation was 6 and 10% respectively for urine and 5 and 8% respectively for plasma. $1,25(\text{OH})_2\text{D}_3$ was determined in 2 ml of serum according to Eisman *et al.* (1976). Samples were extracted with acetonitrile, purified on silica gel cartridges (Sep-pakC18, Millipore) with a flow of 1 ml/min methanol and water (60–40) and then separated by high pressure liquid chromatography (HPLC) (LKB) on a normal phase column (Zorbax sil, Dupont) (Fraherr *et al.*, 1983). Competitive binding assay was performed using a normal chick duodenal receptor (Eisman *et al.*, 1976); 0.5 mg protein/tube gave a reproducible level of $45 \pm 5\%$ zero binding. Mean final recovery, calculated by the addition of a high specific activity H^3 - $1,25(\text{OH})_2\text{D}_3$ (Amersham), was approximately $50 \pm 5\%$. The standard curve ranged from 1.5 to 96 pg/tube and the lower detection limit was 4 pg/ml of serum. The intra-assay and inter-assay coefficient of variation was 8 and 13% respectively.

Urinary data refer to the mean value of two 24-h collections from each diet. Fasting urinary calcium excretion is expressed as mgCa/dl GF (Pak *et al.*, 1975) and both urinary and nephrogenous cyclic AMP as nmol/dl GF according to Broadus *et al.* (1977); all values are expressed as mean $\pm$ SD. The differences between means were calculated by Student's *t* test for paired and unpaired groups.

Results

Minimal criteria for classification

In accordance with other authors (Coe and Kavalach, 1974; Broadus *et al.*, 1978), idiopathic hypercalciuria was defined as a 24-h calcium excretion > 300 mg for men and 250 mg for women, and/or > 4 mg/kg body weight on a 1000 mg calcium diet.

Two hypercalciuric subgroups were identified (absorptive hypercalciuria (AH) and renal hypercalciuria (RH)). The distinction between them was based on the fasting calcium excretion at the end of the 400 mg calcium diet, the level being less than or more than 0.11 mgCa/dl GF respectively (Pak *et al.*, 1975). Absorptive hypercalciuria was further classified on the basis of the calcium excretion levels during a low calcium diet as type I or type II according to whether more or less than 200 mg/day was excreted respectively (Pak *et al.*, 1980).

The following subgroups were also identified:

Primary hyperparathyroidism (PHPT): patients characterised by stable or intermittent hypercalcaemia, normal or high PTH, and also by parathyroid adenoma or hyperplasia detected during surgical exploration of the neck.

Type I renal tubular acidosis (RTA 1): urinary pH > 6 , and hyperchloraemic systemic acidosis.

Hyperuricosuric calcium lithiasis (HUCA): elevated excretion of uric acid but normal calcium excretion. The upper limit for uric acid excretion was defined as 600 mg/day (Pak *et al.*, 1977); however, 6 normal control subjects had higher values.

Enteric hyperoxaluria (EHY): calcium oxalate nephrolithiasis, augmented excretion of oxalic acid (> 44 mg/day) accompanying pathology of the small intestine, or after resection or intestinal bypass.

Primary hyperoxaluria (PHY): increased excretion of oxalic acid (> 100 mg/day) and calcium oxalate stones.

Uric acid lithiasis (UA): detected by stone analysis.

Infection lithiasis (INF): stones of magnesium ammonium phosphate, with no other metabolic abnormalities.

Cystine lithiasis (CY): cystine stones and high urinary excretion of this amino acid.

Lithiasis without any apparent metabolic abnormality (NMA): normal serum and urinary levels for all of the above.

Table 1 reports epidemiological data for each of the 12 groups studied. Most patients were examined for the first time between 30 and 40 years of age. Men predominated in all groups except those with primary hyperparathyroidism and type I renal tubular acidosis. The earliest onset of stones was detected in type I RTA (age 10) and the latest in primary hyperparathyroidism (age 34). The severity of the stone disease, determined by the total number of stones passed and the stone passage rate during

Table 1 Epidemiological Data

Disease	Case no.	Age (years)	Sex (% male)	Age at onset of stone disease (years)	Stones passed (no/patient)		History of urinary infection (%)	History of familial stone disease (%)	Arterial hypertension (%)
					Total	3 years			
Hypercalciuria:									
(a) Absorptive type I	50	37 ± 10	54	25.6	6.0 ± 4.3	2.6 ± 1.8	19	48	10
(b) Absorptive type II	22	38 ± 13	52	26.8	4.5 ± 3.1	1.9 ± 1.0	14	48	14
(c) Renal	30	36 ± 10	80	22.8	8.6 ± 11.7	3.8 ± 4.5	17	43	3
Primary hyperparathyroidism	10	47 ± 16	30	33.5	66.9 ± 141.9	25.3 ± 61.6	40	20	40
Renal tubular acidosis	2	22 ± 14	0	10.5	11.5 ± 12.0	2.5 ± 0.7	0	100	0
Hyperuricosuric calcium lithiasis	11	34 ± 11	91	26.2	3.1 ± 2.2	1.8 ± 1.7	0	54	9
Hyperoxaluria:									
(a) Enteric	3	40 ± 10	66	30	25.0 ± 30.0	7.3 ± 15.0	100	0	0
(b) Primary	2	25 ± 7	50	13	10.5 ± 6.3	3.2 ± 2.1	0	50	0
Uric acid lithiasis	4	30 ± 10	75	20	7.2 ± 7.2	2.5 ± 1.0	0	25	0
Infection lithiasis	4	44 ± 10	75	23	9.2 ± 11	1.2 ± 1.8	100	25	0
Cystine lithiasis	4	23 ± 9	75	14.5	6.5 ± 6.2	4.8 ± 6.8	0	75	0
No metabolic abnormality	38	34 ± 13	50	25	5.6 ± 5.9	2.5 ± 2.5	31	54	5

Values are mean ± SD.

the previous 3 years, was greatest in patients affected by primary hyperparathyroidism.

Urinary tract infection (>100,000 colonies/ml) was present in all patients with either enteric hyperoxaluria or infection stones, in 40% of those with primary hyperparathyroidism, in 18% with

idiopathic hypercalciuria and in 31% of those without apparent metabolic abnormality. There was a familial history of nephrolithiasis in both patients affected by RTA I, in 20% of those with primary hyperparathyroidism, in 50% of those with idiopathic hypercalciuria and also in those without

Table 2 Biochemical Data in Hypercalciuria

	Absorptive hypercalciuria		Renal hypercalciuria	Primary hyperparathyroidism	Renal acidosis	Control subjects
	Type I	Type II				
Serum calcium (mg/dl)	9.50 ± 0.38	9.38 ± 0.40	9.42 ± 0.32	11.46 ± 0.90*	8.86 ± 0.80†	9.58 ± 0.35
Serum ionised calcium (mg/dl)	4.56 ± 0.16	4.52 ± 0.12	4.60 ± 0.18	5.68 ± 0.56*	4.28 ± 0.28‡	4.52 ± 0.12
Serum phosphorus (mg/dl)	3.27 ± 0.39	3.37 ± 0.46	3.38 ± 0.46	2.58 ± 0.48*	3.42 ± 1.23	3.21 ± 0.39
Serum uric acid (mg/dl)	5.02 ± 1.23	4.57 ± 1.38	4.97 ± 1.30	5.50 ± 1.04§	3.17 ± 0.09	4.60 ± 1.03
Serum parathormone (ng/ml)	0.49 ± 0.22	0.49 ± 0.25	0.49 ± 0.28	1.71 ± 1.14*	0.67 ± 0.10	0.40 ± 0.25
Urinary calcium:						
1000 mg Ca diet (mg/24 h)	333 ± 79*	277 ± 56*	381 ± 105*	334 ± 113*	290 ± 184	180 ± 85
400 mg Ca diet (mg/24 h)	269 ± 67*	155 ± 27	290 ± 92*	275 ± 108*	246 ± 174‡	137 ± 56
Fasting (mg/dl GF)	0.07 ± 0.02*	0.07 ± 0.02†	0.14 ± 0.02*	0.17 ± 0.09*	0.20 ± 0.04*	0.05 ± 0.03
Fasting AMPc:						
Urinary (nmol/dl GF)	3.73 ± 1.04	3.60 ± 0.95	3.92 ± 0.93	6.91 ± 2.23*	3.28 ± 0.94	3.55 ± 0.76
Nephrogenous (nmol/dl GF)	2.10 ± 0.92	2.13 ± 0.81	2.37 ± 0.77	5.32 ± 2.05*	1.48 ± 0.37	2.08 ± 0.68
Urinary uric acid (mg/24 h)	521 ± 178	489 ± 184	546 ± 164	468 ± 203	470 ± 130	488 ± 160
Urinary oxalate (mg/24 h)	25 ± 10	23 ± 8	27 ± 6	28 ± 8	20 ± 12	28 ± 12
Urinary phosphorus (mg/24 h)	748 ± 218	551 ± 139	750 ± 249	594 ± 199	492 ± 67	633 ± 169
Total volume (lt/24 h)	1.90 ± 0.71	1.79 ± 0.74	1.94 ± 0.61	1.95 ± 0.76	2.10 ± 0.57	1.60 ± 0.80
*Urinary pH	5.68 ± 0.41	5.65 ± 0.29	5.69 ± 0.49	5.74 ± 0.38	6.30 ± 0.28	5.62 ± 0.50
Ccr (ml/min)	129 ± 11	104 ± 23	116 ± 32	101 ± 29	89 ± 19	108 ± 38

Values are mean ± SD. Significant difference from the control group is represented by * for $P < 0.001$; † for $P < 0.01$; ‡ for $P < 0.02$; § for $P < 0.05$.

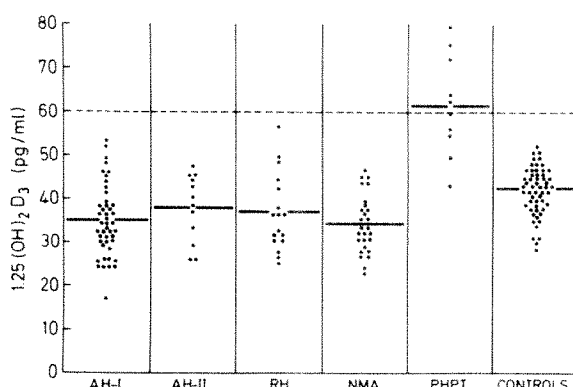


Fig. Serum 1,25-dihydroxycholecalciferol levels in absorptive hypercalciuria type I (AH-I) and type II (AH-II), renal hypercalciuria (RH), primary hyperparathyroidism (PHPT), patients with no metabolic abnormalities (NMA) and 55 normal controls. Dotted horizontal line indicates the upper third standard deviation of the mean

any apparent metabolic disorder. Arterial hypertension—frequently associated with altered calcium transport (Strazzullo *et al.*, 1983)—was found in 40% of patients with primary hyperparathyroidism and in 10% of those with idiopathic hypercalciuria.

Biochemical presentation (Tables 2 and 3)

Total serum calcium, as well as the ionised fraction, was high in all patients affected by primary hyperparathyroidism and was reduced only in those with renal tubular acidosis. Mean values for serum phosphorus were significantly decreased in the hyperparathyroid groups ($P < 0.001$). Serum PTH was normal in all patients, except in those with primary hyperparathyroidism. The Figure reports the values of serum 1,25(OH)₂D₃ in hyperparathyroidism and in 55 normal controls. Serum calcitriol levels were slightly (but significantly) reduced in patients with type I ($P < 0.001$) and type II ($P < 0.05$) absorptive hypercalciuria, as well as in renal hypercalciuria ($P < 0.01$). However, mean vitamin D levels were significantly higher in subjects with primary hyperparathyroidism ($P < 0.001$) and 5 had values above the third standard deviation of controls. In particular, serum calcitriol concentration (pg/ml, mean $\pm$ SD) was 42 ± 5.5 in controls, 34.5 ± 8.2 and 37.7 ± 7.6 in type I and type II absorptive hypercalciuria respectively, 36.2 ± 8.9 in renal hypercalciuria, 34 ± 7.2 in patients without apparent metabolic alterations and 61.1 ± 11.5 in primary hyperparathyroidism. High levels of serum uric acid were found in patients with hyperuricosuric calcium urolithiasis, cystine lithiasis, type I absorptive hypercalciuria and primary hyperpara-

thyroidism, but were significant only in the last group ($P < 0.05$).

A fasting calcium excretion level > 0.11 mgCa/dl GF was detected—as well as by definition in patients with renal hypercalciuria—in a consistent number of patients with primary hyperparathyroidism and in those with type I renal tubular acidosis.

Urinary phosphate was generally higher during the 1000 mg calcium diet than on the low calcium diet, but there was no difference in the various groups when compared with the controls. Urinary sodium excretion, evaluated on the low calcium diet and ranging between 85 and 125 mEq/24 h, did not differ significantly between the groups studied.

The excretion of total and nephrogenous cyclic AMP—measured during the low calcium diet as well as in fasting morning samples—was significantly different from that of the controls only in patients affected by primary hyperparathyroidism ($P < 0.001$).

A uric acid excretion level > 600 mg/day in hyperuricosuric nephrolithiasis was also found in 14 patients with type I absorptive hypercalciuria, in 6 with type II absorptive hypercalciuria, in 2 with uric acid lithiasis and in 1 with cystine lithiasis.

Discussion

This ambulatory protocol has provided a profile for all stone formers on the basis of a presumptive pathophysiological disorder. Hypercalciurics with urine calcium excretion > 0.11 mg/dl GF at the end of a 400 mg calcium diet were considered renal in origin; the fasting urine calcium of absorptive hypercalciurics, although higher than that of controls, was below the cut-off value for renal hypercalciurics. Since this study showed normal parathyroid activity in all hypercalciurics, as well as in the group without any apparent metabolic abnormality, we considered that an oral calcium load test would not contribute useful data for any further classification in terms of serum and urine calcium, serum parathormone and urine cyclic AMP (Pak *et al.*, 1975; Broadus *et al.*, 1978). This may explain the different distribution of our hypercalciurics into subgroups compared with the study by Pak *et al.* (1980). Types I and II AH were equally represented in Pak's series and the RH patients were less than 15% of the total hypercalciuric population. In our study, type II AH cases comprised half of that of type I, and cases of RH represented almost one-third of all hypercalciurics. This may also explain why we did not have the

Table 3 Biochemical Data in Other Groups

	Hyper-uricosuric calciuria urolithiasis	Hyperoxaluria		Uric acid lithiasis	Infection lithiasis	Cystine lithiasis	No metabolic abnormality
		Enteric	Primary				
Serum calcium (mg/dl)	9.32 ± 0.52	9.20 ± 0.48	9.54 ± 0.08	9.34 ± 0.34	9.26 ± 0.40	09.44 ± 0.34	9.40 ± 0.42
Serum ionised calcium (mg/dl)	4.56 ± 0.16	4.48 ± 0.08	4.60 ± 0.04	4.40 ± 0.08	4.40 ± 0.08	4.52 ± 0.04	4.59 ± 0.18
Serum phosphorus (mg/dl)	3.07 ± 0.57	3.10 ± 0.26	3.12 ± 0.24	3.61 ± 0.79	3.65 ± 0.55	3.57 ± 0.83	3.38 ± 0.45
Serum uric acid (mg/dl)	5.54 ± 1.78	4.63 ± 0.65	4.80 ± 0.42	4.61 ± 1.94	5.0 ± 1.1	5.15 ± 1.54	4.61 ± 1.08
Serum parathormone (ng/ml)	0.37 ± 0.18	0.36 ± 0.20	0.35 ± 0.07	0.63 ± 0.26	0.50 ± 0.2		0.50 ± 0.26
Urinary calcium:							
1000 mg calcium diet (mg/24 h)	161 ± 40	180 ± 140	210 ± 43	280 ± 138	140 ± 70	166 ± 97	207 ± 61
400 mg calcium diet (mg/24 h)	143 ± 28	133 ± 30	132 ± 11	223 ± 146	112 ± 50	124 ± 62	151 ± 37
Fasting (mg/dl GF)	0.05 ± 0.02	0.07 ± 0.02	0.05 ± 0.01	0.08 ± 0.05	0.05 ± 0.02	0.08 ± 0.04	0.06 ± 0.03
Fasting AMPc:							
Urinary (nmol/dl GF)	4.03 ± 0.60	3.86 ± 0.90	3.94 ± 0.36	2.85 ± 1.14	3.08 ± 1.0		3.75 ± 0.94
Nephrogenous (nmol/dl GF)	2.59 ± 0.30	2.36 ± 0.77	2.99 ± 0.29	1.37 ± 0.82	1.85 ± 0.7		2.21 ± 0.80
Urinary uric acid (mg/24 h)	936 ± 197*	453 ± 125	540 ± 85	544 ± 258	520 ± 180	477 ± 263	425 ± 169
Urinary oxalate (mg/24 h)	31 ± 11	64 ± 15*	147 ± 26*	23 ± 10	28 ± 6	24 ± 9	26 ± 9
Urinary phosphorus (mg/24 h)	647 ± 158	586 ± 140	448 ± 69	748 ± 210	550 ± 195	566 ± 127	572 ± 134
Total volume (lt/24 h)	1.70 ± 0.54	1.80 ± 0.60	2.75 ± 1.77	2.12 ± 0.30	1.8 ± 0.6	1.32 ± 0.74	1.60 ± 0.48
Urinary pH	5.61 ± 0.40	5.80 ± 0.20	5.90 ± 0.14	5.45 ± 0.36	6.4 ± 1.16†	5.62 ± 0.26	5.68 ± 0.37
Ccr (ml/min)	119 ± 23	103 ± 15	94 ± 21	125 ± 10	85 ± 30	95 ± 32	100 ± 19

Values are mean ± SD. Significant difference from the control group is represented by * for $P < 0.001$; † $P < 0.05$.

subgroup that Pak defined as being of uncertain classification. The evidence of a slight but significant reduction in vitamin D levels in the groups with calcium stones—with and without hypercalciuria—is interesting. Our data differ from those of Insogna *et al.* (1985) and of Shen *et al.* (1977), who reported high vitamin D concentrations, but are closer to the normal levels described by Coe *et al.* (1982) and by Netelenbos *et al.* (1985). We have assayed serum $1,25-(\text{OH})_2\text{D}_3$ during a low calcium diet both in stone formers and in normal control subjects, and the latter group displayed a mean vitamin D concentration similar to that of normal subjects reported by Netelenbos *et al.* (1985) and Broadus *et al.* (1980). It is possible that the lower serum levels of $1,25-(\text{OH})_2\text{D}_3$ are a consequence of suppressed parathyroid activity secondary to increased calcium transport by mucosal cells with abnormally large numbers of high affinity receptors. Therefore, as suggested by Coe and Bushinsky (1984), the flux of calcium from the intestine to the extracellular fluid will increase and the levels of parathormone, tubular reabsorption of calcium and $1,25(\text{OH})_2\text{D}_3$ will be reduced. Bushinsky and Favus (1988) observed a reduction in the active vitamin D levels in balanced hypercalciuric compared with normocalciuric rats and interpreted these results on the basis of increased responsiveness by enterocytes to $1,25-(\text{OH})_2\text{D}_3$ due to a presumptive, genetically

mediated increase in receptor numbers. However, we have no data showing depression of parathyroid function such as reduced serum parathormone and urine cyclic AMP. Another possibility is that in our hypercalciurics, serum calcitriol is reduced by a mechanism related to the altered calcium transport described in such disorders. An altered tissue calcium uptake has been observed by Liberman *et al.* (1968), Coe *et al.* (1982) and also by our group (Nunziata *et al.*, 1989); it has been shown that total body calcium turnover, as well as bone formation and reabsorption, increase through a mechanism independent of renal tubular calcium leakage. Thus it may be speculated that the vitamin D-independent gut-calcium hyperabsorption, the increased body turnover and the slightly reduced $1,25(\text{OH})_2\text{D}_3$ serum levels are interdependent features of the increased tissue calcium uptake. It is not surprising that calcitriol is reduced also in normocalciuric idiopathic stone formers since a clearcut separation between this group and the hypercalciuric population cannot be objectively obtained.

One implication of the above is that idiopathic hypercalciuria associated with recurrent renal calcium calculi represents a homogeneous disorder of calcium handling, characterised by intestinal calcium hyperabsorption not directly dependent on vitamin D levels and with a different degree of

expression—ranging from low for type II absorptive hypercalciuria to high for renal hypercalciuria.

The percentage of subjects affected by hyperparathyroidism is the same as in Pak's study; the diagnostic value of parathormone appears slightly higher than that of nephrogenous AMP, as previously reported (Nunziata *et al.*, 1986). The mean $1,25(\text{OH})_2\text{D}_3$ in this group was high ($P < 0.001$), although some patients had values within the normal range.

In stone patients with hyperuricosuria, urinary uric acid was higher than in the control group, and in any case > 60 mg/day by definition. The urine pH (6.1 ± 0.40 SD) was not significantly different from that of the controls, and similar to that of Coe (1979), but lower than that reported by Pak *et al.* (1980). Sodium excretion ranged between 65 and 150 mEq/24 h and the calcium/sodium ratio was lower than that reported as favouring sodium monourate formation and which is partly responsible for the initial nucleation of calcium oxalate crystallisation (Pak *et al.*, 1977). However, our values occurred with a standardised diet that in some respects may be quite different from the home diet.

Two of 4 patients affected by urate lithiasis had a lower urinary pH (< 5.5) with which an increased uric acid precipitation was correlated (Pak *et al.* 1977). They had a high calcium excretion; 1 patient fulfilled the criteria for type I absorptive hypercalciuria and the other for renal hypercalciuria. The remaining 2 patients had uric acid excretion values > 600 mg/day. Two of 4 patients with cystine stones had increased urinary calcium levels on a 1000 mg calcium diet but these were reduced by a low calcium diet.

Our classification fulfilled the criteria described by Pak *et al.* (1980) and, contrary to the multifactorial origin suggested by several authors, was based on the assumption that metabolic alterations occurring in nephrolithiasis had a pathophysiological significance. Thus hypercalciuria causes urinary oversaturation of calcium, oxalate and phosphate; hyperoxaluria causes saturation of calcium oxalate, whereas hyperuricosuria leads to urinary supersaturation with monosodium urate crystals and crystallisation of calcium salts (Pak *et al.* 1977) as a result of epitaxy. We did not take into account urine crystallisation inhibitors such as magnesium, pyrophosphate, glycosaminoglycans, acid protein (nephrocalcin) and citrate (Pak *et al.*, 1985). Their reduced excretion may nevertheless play an important role in stone formation in the majority of patients characterised above. Most patients have

more than 1 risk factor for stone formation: some hypercalciurics have increased uric acid excretion and hyperoxaluria; hypocitraturia and hyperuricosuria are also associated with more than one abnormality, as this study shows and as has been described by Wilson (1989). The data show conclusively that the hypercalciuric population is as well represented in our study as in that by Pak *et al.* (1980): the fact that the renal subgroup accounts for almost twice the number reported in the series of Pak *et al.* (1980) may be explained on the basis of less selective classification criteria on our part. However, we were unable to confirm 2 points: secondary hyperparathyroidism as a consequence of renal tubular calcium leakage and the increased levels of serum calcitriol reported by some (Shen *et al.*, 1977; Insogna *et al.*, 1985) but not by others (Coe *et al.*, 1982; Netelenbos *et al.*, 1985). Finally, among the other 9 subgroups of stone formers characterised by this protocol, the distribution of patients is similar to that in the series by Pak *et al.* (1980), except for our larger group defined as having no metabolic abnormality. This suggests no consistent differences between the prevalence of pathophysiological mechanisms associated with stone formation between the 2 series.

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Inhibition by Sodium-potassium Citrate (CG-120) of Calcium Oxalate Crystal Growth on to Kidney Stone Fragments Obtained from Extracorporeal Shock Wave Lithotripsy

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Summary—Retention of fragments within the kidney after extracorporeal shock wave lithotripsy (ESWL) continues to be a major shortcoming of this form of stone treatment. The aim of this study was to evaluate the ability of sodium-potassium citrate to inhibit calcium oxalate crystal nucleation and growth on to stone fragments remaining after ESWL. The continuous flow crystallisation technique was adapted to induce calcium oxalate crystal nucleation and growth on to the surface of fragmented kidney stones and the inhibitory effect of sodium-potassium citrate was assessed by scanning electron microscopy and by determining the relative increase in crystalline mass at final concentrations of 0, 2, 4, 6, 8, 10 mmol/l.

Sodium-potassium citrate significantly inhibited the deposition of new crystalline calcium oxalate in a dose-dependent manner above 2 mmol/l; these findings were confirmed by scanning electron microscopy.

It was concluded that sodium-potassium citrate may provide an effective means of preventing the formation of new kidney stones by the deposition of calcium oxalate on to residual stone fragments resulting from ESWL and that the technique used is an efficient means of testing the efficacy of therapeutic agents to prevent stone recurrence in patients treated with ESWL.

Extracorporeal shock wave lithotripsy has revolutionised the treatment of renal stones: high success rates and low morbidities associated with the technique have guaranteed its status as the preferred form of management for most urinary calculi (Lingeman *et al.*, 1986). Nonetheless, the long-term renal consequences of ESWL have yet to be fully documented and there is mounting evidence that in a significant proportion of cases it can cause a range of both peri- and intra-renal injuries and other unexplained abnormalities (Kande *et al.*, 1985). Such damage is associated with an immediate loss of renal function which may be permanent and which may account for the observation that hypertension appears to be an important compli-

cation of ESWL in approximately 8% of patients (Williams *et al.*, 1988). These sequelae have particularly worrying ramifications for younger patients and those in whom further courses of treatment are required. Additional treatment in a significant number of individuals is inevitable: some 50% of patients can expect to suffer symptomatic recurrences of urolithiasis, including 15% who will present within the first year (Mulley *et al.*, 1988). Furthermore, it is ironic that ESWL, which has overcome so many of the drawbacks associated with other surgical approaches to urolithiasis, at the same time may have increased the likelihood of stone recurrence and thereby of re-treatment. Stone shard retention following lithotripsy has featured prominently in the urological literature (Drach *et al.*, 1986; Lingeman *et al.*, 1986; Diederichs, 1987;

Das *et al.*, 1988; Pettersson, 1989; Brownlee *et al.*, 1990), accompanied by the general concern that such fragments may reform into new congeries or serve as nuclei for the formation of new stones. While a number of procedures have been proposed to alleviate the problem of fragment retention, including alterations in body posture (Brownlee *et al.*, 1990), the use of double pigtail ureteric stents and percutaneous procedures (Das *et al.*, 1988) and multiple ESWL treatments (Turk *et al.*, 1987), there is still no completely non-invasive means of satisfactorily eliminating stone fragments from the kidney—especially those lodged in the lower calices (Diederichs, 1987; Pettersson, 1989). The problem is compounded in the 17% or so of cases (Pettersson, 1989) in whom anatomical abnormalities further impede the discharge of particles from the kidney.

One approach which has not been extensively investigated is the use of chemical treatment to prevent or reduce the rate of stone recurrence in individuals subjected to lithotripsy. In recent years a variety of prophylactic agents have been used to reduce recurrences in patients suffering from calcium nephrolithiasis, including hydrochlorothiazide, orthophosphate, alkali-citrates and magnesium. In particular, sodium-potassium citrate has been reported to be effective in the treatment of hypocitraturic calcium nephrolithiasis (Pak *et al.*, 1985; Preminger *et al.*, 1985) and may therefore have application as an inhibitor of further stone formation in patients with residual fragments after lithotripsy. Thus the aim of this study was to evaluate the efficacy of sodium-potassium citrate in preventing the nucleation and growth *in vitro* of calcium oxalate crystals upon the surface of stone fragments passed by patients who had undergone ESWL therapy.

Materials and methods

Fragments of stones were obtained from 10 patients who had been treated with a Siemens LITHOSTAR: infrared analysis demonstrated that more than 95% by weight of the fragments was calcium oxalate. The fragments were thoroughly mixed and 100 mg of the mixture used in each experiment.

A continuous flow crystalliser system was used, incorporating a 75-ml beaker with an internal chamber volume of 50 ml, in which was suspended a membrane-filter cup (COSTAR Transwell; $\approx 0.4 \mu\text{m}$) with a capacity of 5 ml, so that it was fully immersed in the solution. The stone fragments were placed on the membrane filter in contact with the solution in the main reaction chamber (Fig. 1) and

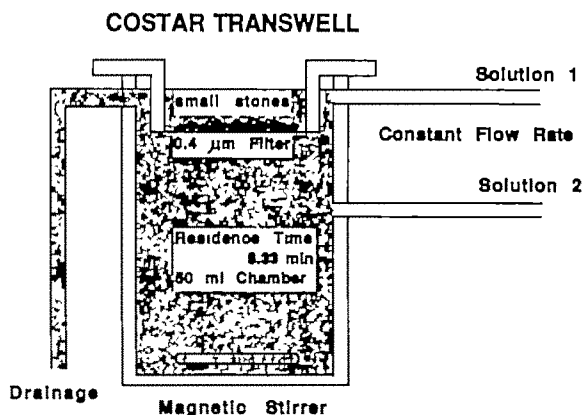


Fig. 1 Diagrammatic representation of the constant composition crystallisation system.

equal volumes of the 2 feed solutions pumped into the chamber using a multi-pump PA-42 (Yamato Co.) at the rate of 3 ml/min. The 50-ml volume of the chamber was maintained by removing the overflow with a vacuum pump.

The composition of the 2 feed solutions, based on those used by Robertson and Scurr (1986), and the final concentration of the various components after mixing, are shown in the Table. The final concentrations of calcium and oxalate were 6 mmol/l and 0.6 mmol/l respectively, while that of citrate varied from 0 to 10 mmol/l. The pH was maintained at 5.8.

The stone shards were left in contact with the artificial urine for 3 h at room temperature, after which time the cup was removed and the filter rinsed with 2 ml of water and then allowed to dry at room temperature for 24 h. The membranes and fragments were then weighed using a Sartorius

Table Composition of Feed Solutions and Final Concentrations of Incubation Solution Components

Feed solution 1	mmol/L	Final values	
$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	12.01	Ca	6.00 mmol/L
Na_2SO_4	34.23	oxalate	0.60 mmol/L
$\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$	5.92	citrate	0–10 mmol/L
NH_4Cl	86.80	Mg	2.96 mmol/L
KCl	162.73	Na	184.90 mmol/L
SDS	0.14	K	81.40 mmol/L
		Cl	252.30 mmol/L
Feed solution 2	mmol/L	NH_4	43.40 mmol/L
$\text{Na}_2\text{C}_2\text{O}_4$	1.20	SO_4	20.10 mmol/L
$\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$	43.59	PO_4	24.85 mmol/L
Na_2HPO_4	6.12	SDS	0.14 mmol/L
$\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$	4.02	pH	5.80
NaCl	231.09		
SDS	0.14		

2004 MP balance and the change in weight obtained by subtraction. At the completion of the experiment the fragments were mounted on stubs, gold-sputtered and examined by scanning electron microscopy using a JOEL JSM-840 scanning electron microscope.

Citrate was added in the form of sodium-potassium citrate (Uralyt-U, Nippon Chemiphar Co. Ltd) and contained 4.5 mmol Na, 4.5 mmol K and 3.7 mmol citrate per gram. All other chemicals used in the study were of analytical grade and were obtained from Sigma Chemical Company Co. (St Louis, USA). Redistilled water was used throughout and the reaction chamber beaker was washed overnight with 1 mol/l HCl after each experiment.

Experiments were repeated to give a total of 6 values at each concentration of citrate. Data were analysed using the Wilcoxon Rank Sum test.

Results

The effect of increasing concentrations of citrate on the mass of crystalline material deposited on to the stone fragments is shown in Figure 2. In the absence of any added citrate the median weight of the stone fragments increased by 4.3 mg. With increasing concentrations of citrate the magnitude of the change in weight of the fragments decreased proportionately; at a concentration of 10 mmol/l the median increase was 1.39 mg. Statistical analysis of the data showed that the results obtained in the presence of 2 mmol/l citrate were not significantly different from those of the control. However, values at all other concentrations were significantly less ($P < 0.001$) than those recorded in the absence of citrate.

Scanning electron micrographs of the stone fragments after the 3-h incubation period are shown in Figure 3. In all cases newly formed crystals are

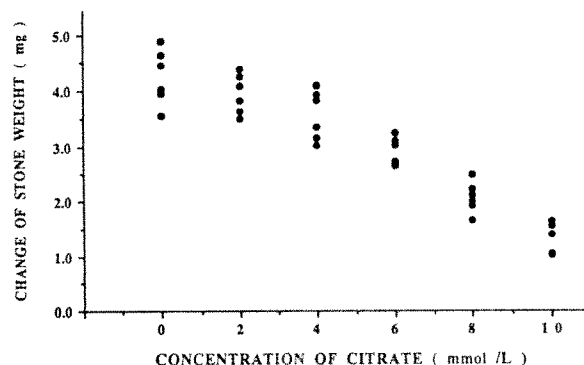


Fig. 2 Increase in stone fragment weight in relation to the final concentration of citrate in the incubation solution.

clearly visible upon the surface of the stone fragments. In the absence of citrate (Fig. 3A) large numbers of calcium oxalate trihydrate crystals were clustered into clumps throughout the entire surface of the fragments, which clearly consisted of calcium oxalate dihydrate. Similar clumps were observed in the presence of 2 mM citrate (Fig. 3B), but the morphology of the individual crystals was less well defined. Calcium oxalate trihydrate was by far the major, if only, crystal type observed in the presence of 4 mmol/l citrate (Fig. 3C) and similar results were obtained at a concentration of 6 mmol/l (Fig. 3D), where the trihydrate was exclusively precipitated. In keeping with the reduced rate of increase in fragment mass observed above, scanning electron microscopy of the fragments in the presence of 8 (Fig. 3E) and 10 mmol/l (Fig. 3F) citrate revealed only very few crystals scattered across the surface of the fragments. Although some of these appeared to exhibit the "bookstack" morphology of the trihydrate habit, most were so small that they could not be categorised at the magnifications used. At the highest citrate concentration the surface appeared to be etched, perhaps reflecting partial dissolution of the fragments.

Discussion

Mixed suspension mixed product removal (MSMPR), or continuous crystalliser, systems have found wide application in research related to kidney stone disease (Miller *et al.*, 1977; Drach *et al.*, 1980, 1982, 1983; Rodgers and Garside, 1981; Robertson and Scurr, 1986; Kohri *et al.*, 1989) since they permit the study of factors affecting the crystallisation of stone minerals at levels of supersaturation comparable to those found in human urine. Although in this study this approach was successfully adapted to study the effects of citrate on the crystallisation of calcium oxalate upon the surface of kidney stone fragments obtained from ESWL, it should be equally applicable to the study of the effects of other therapeutic agents.

Misgivings have long been expressed that further precipitation of stone minerals on to stone fragments inadvertently or unavoidably left after stone surgery or ESWL may act as a source of new stone formation, but to our knowledge there has been no experimental evidence which has directly vindicated the supposition. In this study, however, we have obtained evidence that apprehension regarding the retention of stone fragments may be well founded. Using the modified continuous crystalliser technique, we have shown that stone shards

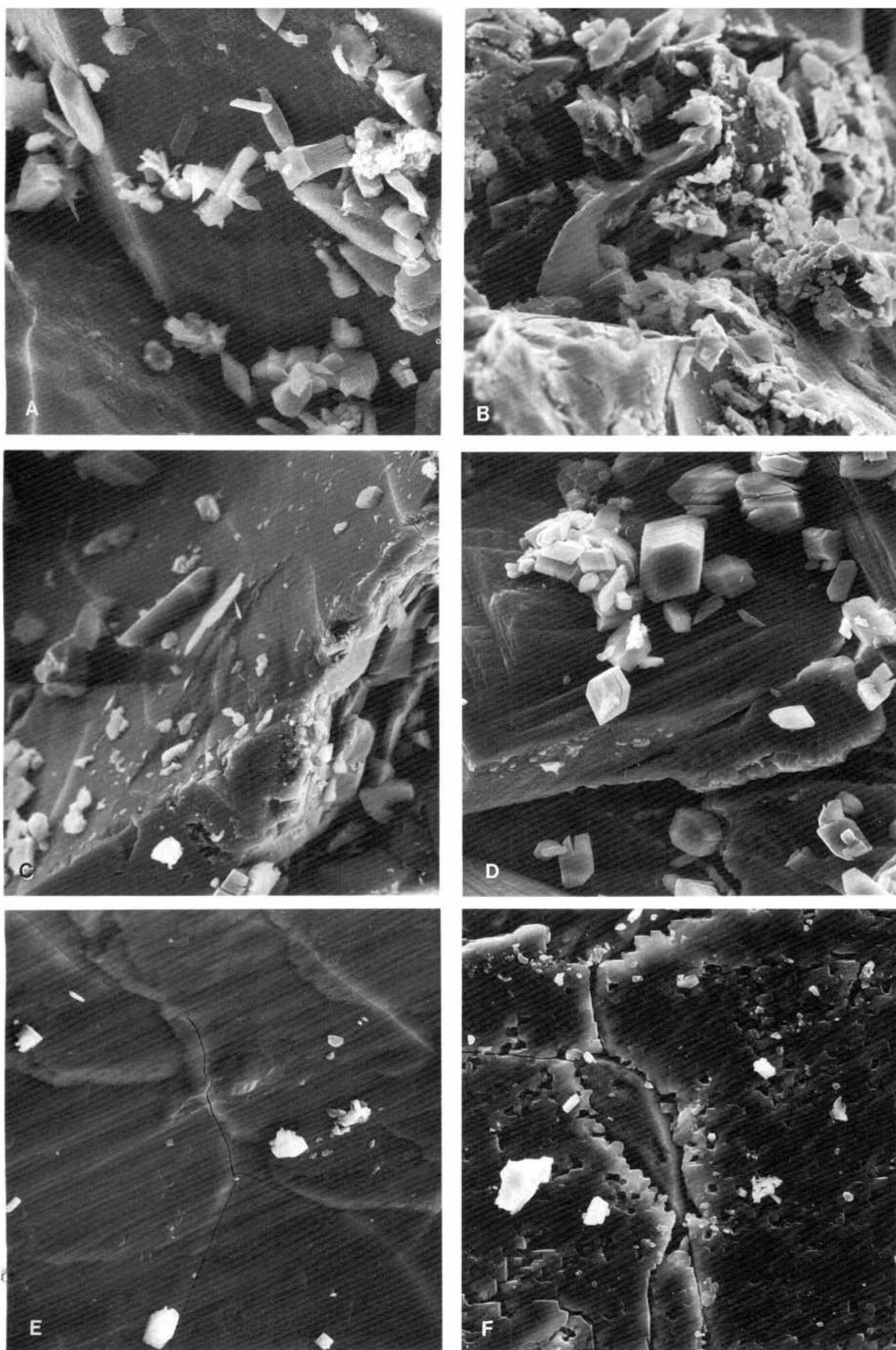


Fig. 3 Scanning electron micrographs of the surfaces of the stone fragments after contact with the incubation solution. (A) Control; 0 mmol/L citrate. (B) 2 mmol/L citrate. (C) 4 mmol/L citrate. (D) 6 mmol/L citrate. (E) 8 mmol/L citrate. (F) 10 mmol/L

resulting from ESWL can support the nucleation and growth of new crystalline material upon their surface. In the samples devoid of citrate the median weight of the shards increased significantly by 4.3%. Although it may be argued that the magnitude of this increase is relatively small, and therefore unlikely to be of significant pathological consequence, it should be remembered that it occurred after an incubation period of only 3 h. Stone fragments are commonly present in a high proportion of patients subjected to ESWL many months after treatment (Lingeman *et al.*, 1986; Diederichs, 1987; Das *et al.*, 1988; Pettersson, 1989) and the opportunity for the deposition of significant quantities of additional stone mineral would presumably reflect the length of time stone fragments remained in contact with supersaturated urine. Growth or reformation into new stones must therefore be seriously considered as a possible consequence of inadequate discharge of stone fragments following lithotripsy.

Although ESWL has often been hailed as the ideal modern solution to an ancient problem, it is at best only a superficial solution; it removes the product, but not the cause of an underlying abnormality, which in approximately 50% of cases will be manifested once more at a later date. Furthermore, results presented here confirm that the retention of residual stone particles following ESWL may increase the already present likelihood of stone recurrences, so that re-treatment may be required in an additional number of cases (and further treatment may not necessarily be in the best interests of the patient). As time has passed, ESWL has come to be associated with an increasing number of significant renal complications (Kande *et al.*, 1985; Mulley *et al.*, 1988; Williams *et al.*, 1988). It is noteworthy, too, that most patients left with clinically significant fragments following lithotripsy refuse the option for further treatment (Das *et al.*, 1988)—presumably for good reasons! It would therefore seem that ESWL is not unreservedly deserving of the reputation it has come to enjoy as a panacea for urolithiasis, and rather than simply fall back on the option of further treatment as the first approach to treating stone recurrences (Turk *et al.*, 1987), it might make more clinical sense to undertake preventive therapy, particularly in patients whose residual fragments promise to be problematic, such as those with structural renal abnormalities (Pettersson, 1989).

The notion of stone prophylaxis is not new and a variety of agents, including thiazide, cellulose phosphate, allopurinol, orthophosphate, magne-

sium and citrate, have been used in attempts to reduce or prevent recurrences in stone formers. In more recent years citrate administration has been increasingly advocated for the treatment of calcium stones (Pak, 1987). The rationale for this advocacy would appear to be based principally on its known inhibitory effects on calcium oxalate crystallisation. Thus citrate has been shown to inhibit the growth and aggregation of calcium oxalate crystals in defined inorganic aqueous media (Meyer and Smith, 1975; Doremus *et al.*, 1978; Ryall *et al.*, 1981; Suzuki and Tsugawa, 1988) and to reduce the amount of calcium oxalate (Hallson *et al.*, 1983; Ryall *et al.*, 1989) and calcium phosphate (Hallson *et al.*, 1983) precipitated from undiluted human urine. Results of the present study have confirmed the inhibitory effect of citrate on the precipitation of calcium oxalate: increasing concentrations of citrate, some of which are achievable during therapy, reduced the amount of calcium oxalate deposited upon stone fragments in a dose-dependent manner, an observation that was borne out qualitatively by scanning electron microscopic examination of the stone fragments. Scanning electron microscopy also revealed that at the highest concentration of citrate tested, 10 mmol/l, the stone shards appeared to be eroded, with pitting clearly evident throughout the surface of all particles. This may have resulted from partial dissolution of the surface by the high concentration of citrate, in keeping with other unpublished studies where we have detected a small reduction in the weight of stone fragments in simple solutions of sodium-potassium citrate. Similar pitting of the stone surface was observed by Khan *et al.* (1986) in fragments of calcium oxalate mono- and di-hydrate stones treated by ESWL inside the body.

The advantages of citrate prophylaxis, including its relative safety during long-term treatment, have been well documented (Pak, 1987). The results of this study would suggest that sodium-potassium citrate therapy may also have application specifically for the prevention of stone recurrence in patients showing evidence of prolonged fragment retention following ESWL, particularly those with anatomical abnormalities. Furthermore, even should further lithotripsy prove necessary in some patients, the use of citrate prior to treatment has the added potential benefit of reducing the number of acoustic shocks to which patients are subjected, by increasing the degree of comminution of the refractory calculi (Akers *et al.*, 1987). This would improve the likelihood of complete elimination of the resulting stone fragments and reduce both the

probability of further stone formation and complications of renal damage.

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A Consumer's Guide to Commercially Available Urodynamic Equipment

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Summary—Eight commercially available urodynamic machines from 6 major manufacturers (Aspen Medical, Dantec, Electro-Medical Supplies (EMS), Uro-gyn, Ormed and Wiest) were assessed for accuracy, construction and user-friendliness. There was < 10% inaccuracy with regard to fill volume, void rate and pressure measurements. The Wiest 6000 plus system was between 11 and 14% inaccurate during voided volume measurement and other systems were < 10% inaccurate. User-friendliness was assessed during routine cystometry and is mainly dependent on the software supplied with the equipment. The merits and faults of each urodynamic system with regard to performing a urodynamic investigation, running a urodynamic service and data management are compared with an "ideal" urodynamic system.

Urodynamic assessment of the lower urinary tract is an established part of modern urological practice. Until recently, urodynamic systems were simple in nature and choice was limited. Today many commercial systems are available, ranging from those which perform simple cystometrograms with paper chart recorders to computerised systems offering more facilities and increasingly advanced automation, albeit at a greater cost. The suitability of a particular machine to the clinician's needs is hard to judge and purchasing a new system is a significant undertaking, since the initial cost ranges from £10,000 to £25,000.

The aim of this study was to assess the accuracy, construction, facilities offered and user-friendliness of each machine currently available from the major manufacturers. Eight systems were tested from 6 manufacturers (Aspen Medical, Dantec, EMS, Uro-gyn, Ormed and Wiest). It is hoped that the results will prove helpful to those involved in choosing new equipment, especially to those involved in establishing a new unit. It was not an aim of this study to recommend one "best buy".

Materials and Methods

All systems were obtained on short-term loan from their suppliers. Manufacturers were invited to install the systems to their satisfaction prior to assessment. Each system was studied in the laboratory setting, according to a predetermined protocol, prior to a 2-week clinical trial in our urodynamics unit. The cost of each system and inclusions were obtained from the manufacturers. No attempt was made to assess long-term reliability.

The construction of each system was assessed and graded according to suitability in 4 sections: waterproofing, general ruggedness, interconnections and electrical safety. As far as possible, these features were assessed using objective measures rather than relying on general impressions. The design of each machine was examined for good electrical practice. Measurements were made of insulation resistance, and earth leakage and earth resistance where appropriate. Relevant labelling was expected and the electrical implications of fluid spillage were considered.

Technical performance was measured with regard to fill volume, voided volume, voiding rate and pressure. The following test methods are themselves reliable to better than $\pm 1\%$ (except for the void

rate, which has an error margin of $\pm 5\%$ at 24 ml/s). Fill volume was tested using laboratory weights 0 to 1000 g in 100 g steps in systems using weight transducers. For pump-only systems the delivered fluid was collected in a measuring cylinder. Voided volume was assessed from 0 to 800 ml in 100 ml increments using a measuring cylinder (with the fluid poured through the flow meter at physiological rates). A simple constant flow device (Griffiths *et al.*, 1983) was used to measure void rate accuracy at 35, 24 and 8 ml/s. Pressure measurement was assessed from 0 to 100 cm H₂O in 10 cm steps against a water manometer.

User-friendliness is hard to assess objectively. By pin-pointing factors which are fundamental to easy use and accurate investigation we hope to have overcome this in our 2-week clinical assessment. The factors chosen, which are not all applicable to every clinician, were graded in comparison to an "ideal urodynamic system" and are listed in Table 1.

The ideal system would be 1-piece, on a good trolley and easily manoeuvrable. It should have been designed for the patient environment, not just a computer on wheels. It should be water- and lubricant-resistant and during investigation there should be no need to use a standard computer keyboard. All controls should be clearly marked with no "hidden" key combinations.

A "checking phase" which displays on screen traces (not transient numbers) to establish the satisfactory position of the catheters and good subtraction prior to commencing the investigation would be ideal. During the study a "pause" facility, where the traces continue to be displayed but the data are not stored, to enable repositioning of catheters, *etc.*, should be available. Variable fill speed during a study is essential. A remote control unit which enables control of the investigation from the patient's couch is an advantage, especially in single-handed urodynamics. If on screen video-mixing is available it should be arranged in such a way as to avoid the superimposition of the traces, the video image and the "on-screen" information, as this may lead to loss of information, particularly from the video image.

Real time printout is an advantage in the event of malfunction and subsequent data loss which otherwise would have resulted in repeat investigation. This facility also enables initial results to be given quickly to the patient, allowing a full analysis to be performed when convenient, *e.g.* after completion of the session, if data storage is

incorporated. To facilitate visual interpretation the printout should be of good size, with graphical markings throughout the trace both of the values measured and a time scale.

The ideal system would automatically present an accurate interpretation of the data, which would be stored permanently in a rapidly accessible and organised fashion. This is not possible at present because of computers' inability to recognise and ignore artifacts which occur during most investigations.

Results

The results of the assessment of construction and design for each system are summarised in Table 2. Weak points included poor trolleys, unprotected interconnections and inadequate waterproofing.

In clinical urodynamic practice a measurement accuracy of $\pm 10\%$ is considered satisfactory. All systems tested were on this basis adequate with regard to fill volume, voided volume, flow rate and pressure with the exception of the Wiest Urocompact 6000 plus flow meter, which was between 11 and 14% inaccurate regarding voided volume (Table 2). Flow rate measurements were based on constant flows, but in the clinical situation this is not the case. Changes in flow rate can precipitate artifacts dependent upon the technology used. The Aspen GR860 system flow meter has a long response time that results in heavily smoothed traces with resulting loss of detail. The EMS System 7 suffered from artifactual oscillations in flow rate caused by waves in the collecting vessel.

A graded summary of the user-friendliness assessment, compared with an ideal system, is shown in Table 1 and cost of the equipment in Table 3.

Discussion

When choosing a urodynamic system it is important to remember the rigours of the patient environment, with fluid and lubricant spillage, and also the implications of movement of the system around the hospital. General ruggedness, waterproofing and suitable interconnections are essential for long-term faultless service.

In urodynamic investigations a measurement accuracy of $\pm 10\%$ is satisfactory in clinical practice. On this basis all systems tested gave adequate performances with the exception of the flow meter in the Wiest Urocompact 6000 plus (Christmas *et al.*, 1989).

Table 1 User-friendliness in the Clinical Situation

	Chart recorder Ormed UIS 5000		Dedicated microprocessor		Personal computer based				
	Dantec Menuet	Wiest Urocompact 6000 plus	Dantec UD 5500	Aspen Medical GR 860 U	Micromedics System Seven	Ormed UIS 6000	Uro-gyn UDS 1002		
Design									
1. Portability (number of pieces)	0 (3)	++ (1)	-- (4)	0 (3)	0 (2)	-- (3)	-- (3)		
2. Suitability to patient environment	0	+	0	++	--	++	+		
In use									
3. Labelling of controls	++	0	+	+	-	++	-		
4. "Check" phase	++	++	++	++	++	++	++		
5. Pause phase	N/A	0	-	-	0	+	++		
6. Adjustable fill speed (during test)	++ (gravity)	++ (pump)	++ (pump)	0 (pump)	++ (gravity)	++ (pump)	++ (pump)		
7. Remote control	0 (optional)	n/a	n/a (foot ped)	n/a (pat. unit)	n/a	++ (cable)	+		
8. Video split screen	++ (optional)	n/a	n/a	++	n/a	n/a	+		
Report									
9. Real time print out	++	--	--	++	--	++	++		
10. Graphical markings	++	--	-- (narrow)	++ (narrow)	--	--	++		
Data management									
11. Post processing	n/a	0	-	0	+	+	++		
12. Data base facilities	n/a	n/a	n/a	n/a	+	++	++		

Key to ratings ++ 0 -- --
best ← → worst

Table 2 Construction and Accuracy

	Chart recorder		Dedicated microprocessor		Personal computer based			
	Orimed UDS 5000	Danisco miniplot	Wheat Urocompact plus	Danisco UD 6000	Danisco UD 5500	Aspen medical GR 860U	Micromedica system	Orimed UDS 6000
Construction								
1. Waterproofing	0	++	+	++	++	-	++	++
2. Ruggedness	-	++	+	++	++	-	-	++
3. Interconnections; suitability	--	++	++	++	++	-	+	+
4. Electrical safety	+	++	++	++	++	0	++	+
Measurement performance								
5. Fill volume (0-1000 ml)	++	+	++	++	++	++	++	++
6. Void volume (0-800 ml)	++	0	-	++	++	++	+	0
7. Void rate (35, 24 and 8 ml/s)	+	++	+	++	++	0	0	+
8. Pressure (0-100 cm H ₂ O)	++	++	++	++	++	0	+	+

Key to ratings ++ 0 --

best ← → worst

Key to accuracy ++ + 0 --

1-30% 4-7% 8-10% 11-14% 15+%

Table 3 Price in United Kingdom in June 1990 and Options (excluding VAT)

<i>Measurements</i>	<i>Chart recorder</i>	<i>Dedicated microprocessor</i>	
	Ormed UJS 5000 Price £9,580	Dantec Menuet Price £11,950	Dantec UD 5500 Price £18,500 Video system £38,000
Filling	Weight transducer	Peristaltic pump or weight transducer	Peristaltic pump
Pressure	Fluid filled lines	Fluid filled lines	Fluid filled lines
Flow	Dipstick (needs priming)	Spinning disc	Spinning disc
Options	Catheter withdrawal device £440 Syringe driver £805 Remote control £80 Compudyn £2995 (enables report generation and video studies)	UPP module £257 Catheter withdrawal device £948 EMG module £1044	Colour plotter £3,114 Software for PC £933 to £1,399
<i>Personal computer based</i>			
	Aspen Medical GR 860U Price £20,076	Micromedics System Seven Price £11,750	Uro-gyn UDS 1002 Price £22,450 Video system £32,200
Filling	Weight transducer	Weight transducer and peristaltic pump	Weight transducer and peristaltic pump
Pressure	Optional	Fluid filled lines	Optional
Flow	Pressure measurement	Dipstick (needs priming)	Weight transducer
Options	Pressure transducers £500-£2,000	Catheter withdrawal device £750 Data base £1,875	Cavernometry £3,750 Rectomanometry £2,500
			EMG module £600

There has recently been a strong trend towards computerisation in the equipment commercially available. Ease of use is heavily dependent on the software supplied. All systems had adequate "checking phases" prior to commencing investigation. The "pause" facility was generally poorer. In this mode the Dantec UD5500, the EMS System 7 and the Wiest Urocompact 6000 plus did not display any pressures to aid repositioning of catheters, etc. The Dantec Menuet and Aspen GR860U displayed figures but not traces. In the Ormed 6000 the traces continued but the pump or withdrawal device was stopped. The most comprehensive "pause" facility was found in the Uro-gyn UDS 1002, where the full display continued and it was possible to record events up to 40 s after they had occurred.

Computerisation has obvious advantages in that results can be automatically generated and the data collected can be stored for future review and research. However, there are major pitfalls in the automatic generation of figures which will result in diagnostic errors. This stems from an inherent inability of the systems to recognise artifacts in the acquired data. Analysis of the data depends on the identification of key "events", e.g. maximum detrusor pressure during the filling phase and the onset of flow. This makes the review of all results and if necessary the repositioning of "EVENTS" an essential part of computerised urodynamics. Three different techniques are used to avoid the erroneous selection of an artifact. Firstly, the data are edited during and after the investigation, thus erasing the artifacts before automatic analysis (Uro-gyn UDS 1002). Secondly, the "events" are automatically selected by the data analyser but they can be repositioned by the investigator following critical review (Dantec Menuet and 5500, EMS System 7 and Wiest Urocompact 6000 plus). Thirdly, the events are all investigator-positioned on review and these subsequently form the basis of result generation (Aspen GR860U and Ormed 6000). The assessment of this important facility is reflected in the grading for post-processing (Table 1).

Long-term data storage enables the comparison of subsequent investigations following therapeutic

procedures to assess efficacy; it also facilitates research. It can take the form of floppy discs which are slow to reload and expensive (Dantec Menuet), hard discs which are quick but of finite capacity (Aspen GR860U, EMS System 7, Ormed 6000 and Uro-gyn UDS 1002) and, recently, optical discs. The data stored can include merely the traces or additional information in the form of a full database (Ormed 6000 and Uro-gyn UDS 1002). The need for long-term data storage and databases is dependent upon the type of urodynamic service that is undertaken and is more applicable to large centres and to research activities.

We have presented our assessment of available commercial systems. Selecting a urodynamic system is a compromise based on available funding, the needs of the clinician and the lack of an available perfect system. It was not our intention to recommend one "best buy". The computerisation/automation of systems is widespread and has advantages, e.g. data storage, but critical review of the results automatically generated is essential to prevent error. We are not in the era of automatic diagnostic urodynamics.

Acknowledgements

We thank the suppliers of the urodynamic equipment for their help and co-operation.

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Single-increment Dilatation for Percutaneous Renal Surgery: An Experimental Study

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Summary—Renal nephrostomy track dilatation is an integral part of percutaneous renal surgery. The traditional method has employed sequential dilators of increasing size, or balloon dilatation. This study used a canine model to investigate the effects of single-increment renal track dilatation to 24 F and compares it with the conventional techniques. Single-increment dilatation proved to be a safe technique with minimal haemorrhage or parenchymal damage and healing at 6 weeks by a fine linear scar. It was as safe as conventional techniques. We believe this study proves that single-stage dilatation is a safe technique for use in humans.

An integral part of percutaneous renal surgery is the dilatation of the track to provide an adequate working channel. Dilatation of the track has usually been performed as a multi-increment procedure, commencing with a needle puncture into the collecting system followed by insertion of a guide wire. Once the wire has been placed, dilatation is performed using multiple incremental flexible exchange dilators (Segura *et al.*, 1983), balloon dilators (Clayman *et al.*, 1983; Reddy *et al.*, 1985) or metal telescoping dilators (Alken *et al.*, 1981; Ekelund *et al.*, 1986). The track was usually dilated to 24 to 30 F. Webb and Fitzpatrick (1985) developed a canine model to study the effect of multi-increment dilatation (MID) on the kidney and demonstrated it to be safe.

Despite this, MID in adults has a number of problems. It is time-consuming, guide wire displacement and kinking during exchanges is possible and bleeding may occur from the untamponaded track between exchanges. Balloon dilatation, while decreasing the number of exchanges, still requires multiple exchanges (Clayman *et al.*, 1983).

Rusnack *et al.* (1982) described a single-increment dilatation (SID) using a dilator with a long ureteric extension of 8 F. Webb (1990) developed a

different single-increment dilator, without the ureteric extension, which has proved useful in developing a track in adults for Y-puncture, caliceal divertula and staghorn calculi. Its advantages over MID were that it was possible to perform the dilatation in a confined space, the need for a stable guide wire was less critical, it was fast and there was minimal bleeding.

We have been involved in the adaptation of percutaneous renal surgery to paediatric patients. Two major problems became evident. Firstly, children have a small intrarenal collecting system and hence there is difficulty in establishing and maintaining a guide wire. Secondly, small volume blood loss in children is significant by virtue of their small total blood volume. We believe that SID may help to minimise these problems. This experimental study was performed to evaluate the technique and safety of single-increment dilatation of the kidney.

Materials and Method

A single-increment dilator was manufactured for this study by Cook Urological®. It was made of stiffened PVC, pencil-shaped and fitted snugly over a conventional 0.038 inch diameter guide wire. The leading taper comes to a fine point and is glass polished to reduce friction as it dilates the paren-

chyma. A canine model was used. The animals were given a halothane/N₂O general anaesthetic. The kidney was mobilised via a subcostal incision and delivered through the wound. A 6 F fascial dilator was introduced through the maximum renal convexity into the collecting system. A 0.038 inch diameter guide wire was passed through the dilator into the collecting system and the fascial dilator was removed. The dilatation system of choice was used and the track was dilated to 24 F. After dilatation, a 25 F Amplatz sheath was introduced into the collecting system over the dilator. The kidney was then observed for several minutes and the sheath was then removed. Some kidneys were harvested for immediate evaluation; in other animals the kidney was replaced, the wound closed and the animal awoken. These surviving kidneys were harvested under general anaesthesia at 48 h to study the acute inflammatory response and in others at 6 weeks to study the acute inflammatory response and in others at 6 weeks to study the long-term healing (Table). In this study we compared SID with conventional techniques of dilatation, multi-increment (2 F) Amplatz dilators, balloon dilators and metal telescoping dilators. In the SID group 5 kidneys were evaluated immediately, 4 at 48 h and 2 at 6 weeks. In the conventional dilatation group all were studied immediately. We performed 3 multi-increment dilatations, 2 metal telescoping dilatations and 3 balloon dilatations. The kidneys were evaluated by the following methods: operative observations, intravenous urography (IVU) at 48 h and 6 weeks in the surviving animals, observations of the macroscopic specimen, histological sections stained with haematoxylin and eosin, methyl salicylate sections after latex injection, barium latex angiograms and methyl methacrylate corrosion casts. All animals were cared for in the Animal Research Laboratory at the Royal Children's Hospital. The study protocol was approved by the Royal Children's Hospital Animal Experimentation Ethics Committee and we adhered to the

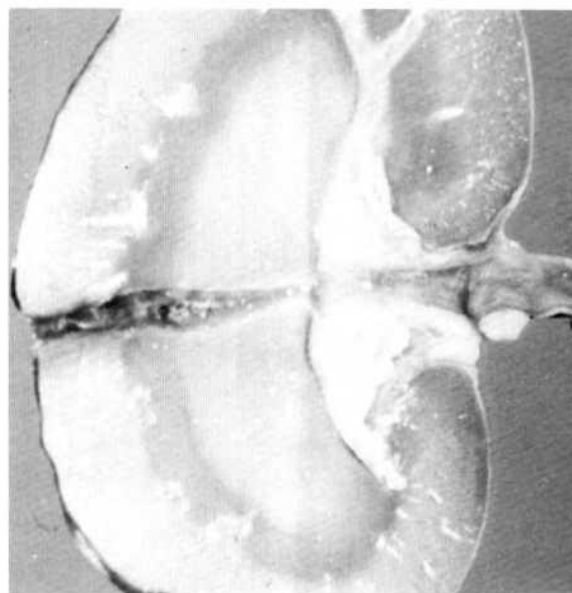


Fig. 1 Macroscopic specimen immediately after single-increment dilatation.

National Health and Medical Research Committee of Australia's ethical guidelines for animal research (NHMRC, 1985).

Results

Single-increment dilatation

The operative technique was reproducible and had no complications. It was apparent that rotating the dilator facilitated its' passage through the capsule into the kidney. There was minimal bleeding and no major parenchymal splitting. Macroscopic section of the immediate evaluation kidneys revealed minimal damage in the vicinity of the track (Fig. 1). Microscopic examination demonstrated a thin exudate on the surface of the track with minimal disturbance of the underlying parenchyma. Barium sulphate latex angiograms did not demonstrate any major segmental vessel damage but did reveal minor peripheral vascular damage (Fig. 2). The kidneys evaluated at 48 h demonstrated similar findings except that the track was plugged with blood clot and debris, with a mild inflammatory reaction at the edge of the track. IVU at 48 h using a double contrast infusion technique did not demonstrate any parenchymal or collecting system damage. The kidneys evaluated at 6 weeks were normal, except for a fine radial scar visible on macroscopic and microscopic examination (Fig. 3). Angiograms and IVU were normal.

Table Breakdown of Dilatation Techniques and Time of Study of 19 Kidneys

Type of dilatation	Time of study		
	Immediate	48 h	6 weeks
Single-increment	5	4	2
Multi-increment	3	—	—
Balloon	3	—	—
Metal telescoping	2	—	—

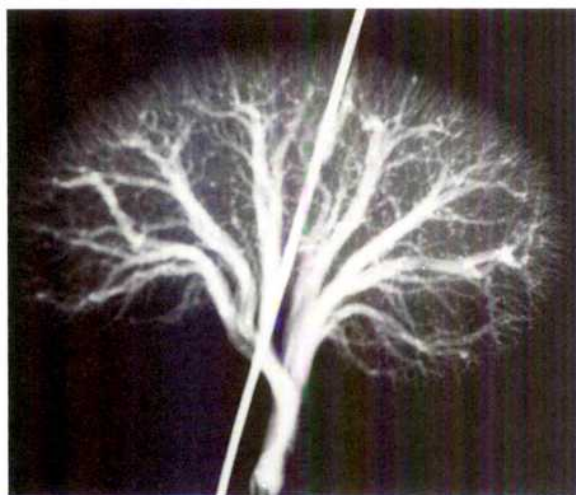


Fig. 2 Barium sulphate latex angiogram immediately after single-increment dilatation. The guide wire was left *in situ* to indicate the track site. A small subcapsular haematoma was present but there was no major vascular damage.

Conventional technique group

Evaluation of this group demonstrated that all 3 of these methods were time-consuming, with mild to moderate oozing occurring between exchanges. The Amplatz sheath was subjectively less stable after MID than in the SID track group. The balloon dilatation technique involved a surprising number of exchanges. The track had to be initially dilated

to 8 F to accommodate the deflated balloon. After the balloon had been inflated and deflated, it was also removed and exchanged for a 24 F Amplatz type and sheath in order to position the sheath in the kidney. Mild to moderate oozing occurred between these exchanges. It was observed that in order for balloon dilatation to be effective, the leading 2-cm tip of the inner core of the balloon must be inside the collecting system or the balloon would inflate outside the kidney. Evaluation of these kidneys revealed minimal damage, similar to that following the other MID techniques.

The metal telescoping dilator technique was simple, although during dilatation it was difficult to control the position metal rod. Bleeding was minimal. These dilators had a flat non-tapered leading edge and the larger dilators caused indentation of the renal capsule before entering the parenchyma, tending to push the kidney away. When performed as a closed procedure this may make dilatation difficult and compromise dilatation where little guide wire is in the kidney. Once again the parenchymal damage was minimal.

Comparison of the damage caused by SID and conventional techniques immediately following track dilatation did not reveal any major differences. No technique caused any major parenchymal splitting or damage to the collecting system.

Discussion

Percutaneous renal surgery is now a well established technique which has acceptable levels of morbidity and mortality (Segura *et al.*, 1983; White and Smith, 1984; Charig *et al.*, 1986; Ekelund *et al.*, 1986; Reddy *et al.*, 1986). Conventional techniques of track dilatation have used either some form of sequential incremental dilator or a balloon dilator. However, these techniques have limitations when confronted with a collecting system with minimal space or where one cannot advance the guide wire to the renal pelvis and ureter, as is often the case with stones in a caliceal diverticulum or a large staghorn calculus. Rusnak *et al.* (1982) described a single-increment dilator and Castaneda-Zuniga *et al.* (1982) reported its use in 25 patients, dilating the track up to 50 F, in some instances without untoward complications. However, this single-increment dilator had a long leading tip which had to be passed down the ureter; hence it was unsuitable for confined space situations. We have previously developed a single-increment dilator for use in these situations in adults, without significant complications (Webb, 1990). We are now involved

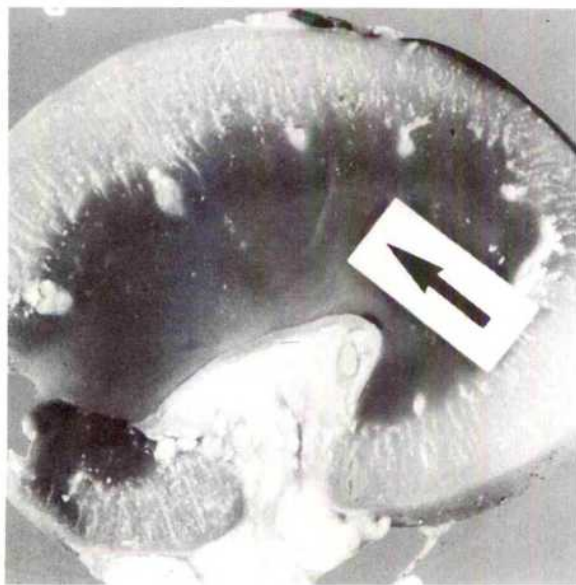


Fig. 3 Macroscopic specimen 6 weeks after single-increment dilatation. The arrow indicates the fine linear scar which was the only evidence remaining of the track.

in the adaptation of percutaneous surgery to children. A major problem is the physical size of the collecting system, which creates difficulty in establishing and maintaining a guide wire for MID. Single-increment dilatation appeared to be the solution to this problem. In this study we have evaluated the damage caused by a single-increment dilatation to 24 F. We demonstrated that the damage was minimal, both immediately and at 6 weeks, and no major parenchymal splitting occurred. When comparing SID with conventional techniques we found that the damage caused was similar. We did not evaluate any long-term conventional dilatations as the immediate results were identical to those of previous reports which included a 6-week follow-up (Webb and Fitzpatrick, 1985). It was interesting that we gained the subjective impression of less bleeding with the SID technique, which is important in paediatric cases. Certainly the SID technique was the simplest and quickest.

Most paediatric percutaneous surgery can be performed with a 20 or 22 F track and we believe that single-increment dilatation is a safe technique in children. We recommend its use in cases involving compromised or difficult access, gross hydronephrosis, supracostal approach and the majority of paediatric cases. We have now used this method in all cases of adult and paediatric (n=21) percutaneous renal surgery for the last 18 months.

The technique has been simple and faster than serial dilatations. It has provided excellent tamponaded access to all regions of the kidney without complications, including 2 children under the age of 6 months.

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Ambulatory Monitoring and Electronic Measurement of Urinary Leakage in the Diagnosis of Detrusor Instability and Incontinence

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Summary—The ability of conventional artificial filling urodynamic studies (CMG) and ambulatory monitoring during natural bladder filling (AM) to detect phasic detrusor activity (detrusor instability) and incontinence was studied in 52 patients suspected on clinical grounds of having bladder dysfunction, but in whom a CMG had not provided an adequate explanation of their symptoms. Detrusor instability (DI) was found on AM in 31 patients who were not unstable on conventional CMG using the criteria of the International Continence Society: DI was diagnosed on filling in 20 patients and on provocation in a further 11. Incontinence was demonstrated by electronic nappy testing in 23 patients: 13 had urge incontinence due to DI, 7 had genuine stress incontinence alone and 3 had both genuine stress incontinence and detrusor instability.

Thus DI was diagnosed significantly more frequently by AM than by CMG. Ambulatory monitoring was more sensitive in the diagnosis of instability and incontinence and it may prove to be a valuable aid in the diagnosis of bladder dysfunction not detected during conventional cystometry.

Patients with involuntary detrusor contractions and distressing symptoms of urinary incontinence, urgency and frequency remain a common and difficult group of patients for the urologist to manage. Using conventional artificial filling cystometry, these contractions were reported by Hodgkinson *et al.* (1963) and the term "detrusor instability" was coined by Bates (1971), who described the relationship between detrusor instability and incontinence. In addition, detrusor instability is a major risk factor for poor outcome after colposuspension (Arnold *et al.*, 1973; Stanton and Cardozo, 1979) and prostatectomy. Nevertheless, the relationship of detrusor instability to urinary symptoms is unclear, since it can be found during conventional cystometry in asymptomatic

patients if provocation tests such as filling with iced water are used.

At the Freeman Hospital, 1600 conventional cystometrograms are performed each year and approximately 400 are carried out in the investigation of patients with suspected detrusor instability; most of these studies provide a satisfactory diagnosis. However, there are patients who have persistent symptoms suggestive of detrusor instability in whom conventional cystometry fails to demonstrate any abnormality. We have developed an ambulatory monitoring system for measuring bladder pressures during natural bladder filling and for the simultaneous detection of urine loss. This study presents the results obtained using this ambulatory monitoring system to investigate 52 patients in whom repeated cystometrograms had failed to explain their persistent symptoms suggestive of detrusor instability or in whom unexpectedly high volumes of urine loss were found on Urilos testing in those with incontinence. It addresses the

Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

question of whether ambulatory monitoring is more sensitive than conventional urodynamic studies in detecting detrusor instability and urinary incontinence.

Patients and Methods

The study group comprised 52 patients (16 male, 36 female; age range 22–74 years) who were investigated by means of ambulatory monitoring of bladder pressures during natural bladder filling (AM); 28 patients complained of symptoms of frequency and urgency, 15 complained of frequency, urgency and urge incontinence, 4 complained of persistent irritative symptoms following prostatectomy, 2 had enuresis and 3 complained of symptoms of stress incontinence alone.

A total of 43 patients had undergone at least 2 conventional cystometrograms (CMG) and 9 had undergone only 1 such test. No abnormality had been demonstrated in 32 patients. Of the remaining 20, unstable detrusor contractions with an amplitude of 10 to 15 cm H₂O were found in 4 patients and unstable detrusor contractions with an amplitude of 5 to 10 cm H₂O were found in 7. One patient with persistent symptoms following prostatectomy had low bladder compliance on medium filling cystometry. Genuine stress incontinence was found in the remaining 8 patients; these patients were investigated by AM because of unexplained frequency and urgency or an unexpectedly large volume of urinary incontinence during Urikos testing.

Conventional cystometry was performed in a purpose-built room containing the equipment for simultaneous cystometry and radiology. In addition to the patient, the room contained the clinician, a nurse and a radiographer. Fluid-filled lines 4F in diameter transmitted bladder and rectal pressures to external transducers; the bladder was filled via a 10F urethral catheter at 100 ml/ml until the patient felt full. Provocation tests such as standing, coughing, straining, heel bouncing and running a tap were used.

The ambulatory monitoring studies were performed using the system described previously (Griffiths *et al.*, 1989). Bladder and rectal pressures were recorded by transducers mounted on 6F catheters. The signals were sampled and digitised at 1 Hz and stored in solid state memory contained in a box weighing 0.75 kg (which the patient could easily carry on a shoulder strap). A third channel was used to record the output from a Urikos

electronic nappy (Urikos pad). The patients recorded voided volumes, and post-micturition volumes were measured by ultrasound. A standard regime was instituted for these investigations: the patient was asked to rest for the first hour of the test, having returned to the ward; in the second hour the patient was active and fully mobile, and the third hour we used provocative tests such as lifting full bags, walking upstairs, standing from a sitting position, coughing, running a bath, washing up or any other action which in the past had caused symptoms of incontinence.

The traces were analysed for the presence of detrusor instability using the standard criteria of the International Continence Society (ICS) (Abrams *et al.*, 1988). These contractions were graded using the classification proposed by Cooleaet (1985) as low amplitude: 5 to 10 cm H₂O; medium amplitude: 10 to 15 cm H₂O; high amplitude: >15 cm H₂O. The association between unstable contractions, symptoms and incontinence was noted.

Results

Detrusor instability on ambulatory monitoring

A total of 31/52 patients (60%) had detrusor instability diagnosed by ambulatory monitoring despite having a stable detrusor on CMG (Figs 1 and 2); 11 of the 31 had borderline instability on CMG (pressure <15 cm H₂O) and all were clearly unstable on AM (>15 cm H₂O), but the remaining 20 patients were unstable on AM despite being completely stable on CMG. The detrusor instability in these 31 patients was detected on filling in 20 patients but only on provocation tests in 11.

The pattern of phasic activity observed during AM was variable. The 11 patients who had borderline unstable contractions on CMG (<15 cm H₂O) had symptomatic unstable contractions during filling on AM. Each of the 11 patients showed phasic contractions with a pressure >15 cm H₂O at a frequency of 2 to 8 contractions per natural fill (median 7); 9 of these patients (81%) also had phasic contractions of 5 to 15 cm H₂O. These low pressure contractions accounted for about 13 to 50% of all contractions (median 14%).

The 20 patients with DI identified only on AM and who had no evidence of phasic detrusor contractions on CMG had unstable detrusor contractions on AM with an amplitude >15 cm H₂O. In 9 of these 20 patients these contractions were seen during filling at frequencies of 2 to 12

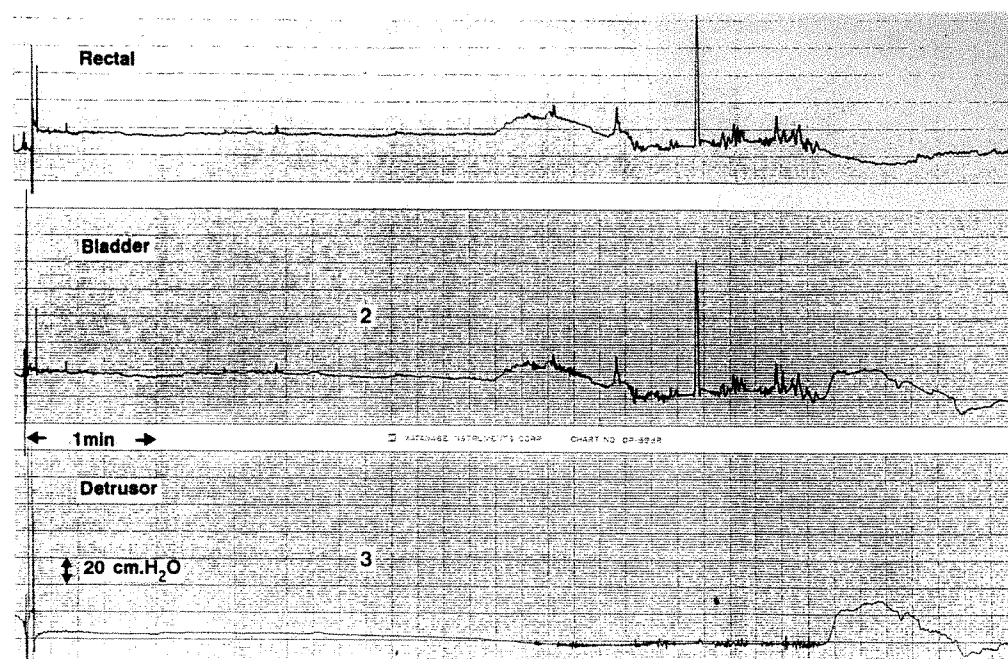


Fig. 1 Conventional cystometrogram from a patient complaining of frequency, urgency and incontinence demonstrating a stable filling phase.

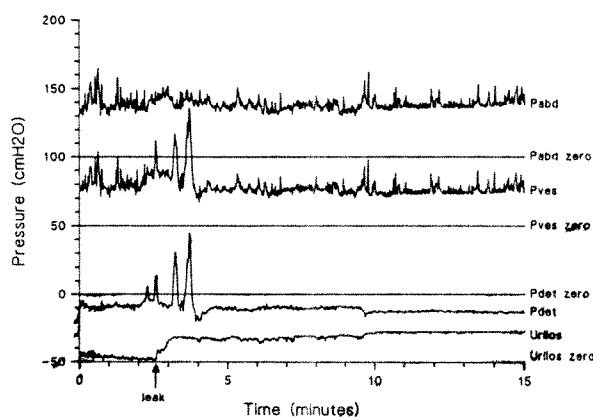


Fig. 2 Part of the ambulatory monitoring study on the same patient in Fig. 1, demonstrating detrusor instability and urge incontinence recorded by the Urilos nappy.

contractions per natural filling phase. Phasic detrusor contractions with an amplitude <15 cm H_2O were seen in 7 of these 9 patients at rates of 17 to 38% of all contractions. In the remaining 11 patients, instability was diagnosed on provocation testing during AM. Following provocation, 1 to 5 unstable contractions were seen: the proportion of contractions >15 cm H_2O varied between 1/1 (100%) and 2/4 (50%) (median 3/5; 60%).

In the 32 patients in whom no abnormality was demonstrated during CMG, unstable detrusor contractions were demonstrated in 16/32, genuine stress incontinence was found in 2 patients, 1 patient had a combination of GSI and DI, and no abnormality was found in the remaining 13 patients.

Of the 8 patients who had genuine stress incontinence (GSI) on CMG, 5 were confirmed to have GSI on AM (Fig. 3), 2 patients had a combination of GSI and DI and in 1 patient no abnormality was demonstrated during AM. Of the 4 patients with post-prostatectomy symptoms, 2 had detrusor instability alone during AM, 1 had GSI and the fourth had no abnormality. Of the 2 men with DI, all contractions were >15 cm H_2O at frequencies of 18 to 26 contractions per hour during filling. No abnormality was found either on CMG or AM in the 2 patients complaining of enuresis.

Urinary incontinence

Incontinence was demonstrated in 23 patients by the electronic Urilos pad during AM. In 13 patients this was urge incontinence which was clearly associated with unstable contractions on ambulatory pressure measurement (Fig. 2). Genuine stress incontinence was demonstrated in 10 patients; in 7 of these this was genuine stress incontinence alone

(Fig. 3), a further 2 patients had a combination of urge incontinence due to instability and genuine stress incontinence, and the remaining patient had detrusor instability which resulted in no loss of urine plus genuine stress incontinence.

Therefore of the 52 patients, 11 patients (who had unstable detrusor contractions on CMG which failed to reach ICS criteria) were unstable on these criteria during AM and 20 further patients who were completely stable on CMG were also unstable on AM. Genuine stress incontinence was found in 1 patient only on CMG but was found during both investigations in 7 patients (in combination with DI in 2 of them) and only on AM in a further 3 patients (in combination with DI in 1 of them).

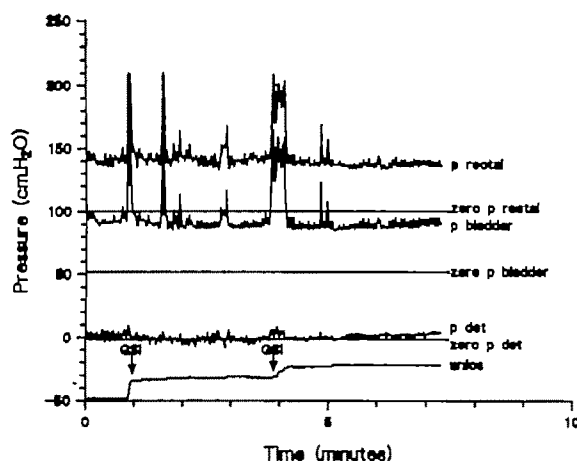


Fig. 3 Part of an ambulatory monitoring study demonstrating genuine stress incontinence.

Discussion

Our findings suggest that ambulatory monitoring during natural bladder filling is able to demonstrate detrusor instability in about half of a group of highly selected patients who had severe persistent symptoms of frequency and urgency but in whom only minor abnormalities were detected on repeated conventional cystometry. This study was not designed to compare the sensitivity and specificity of the 2 techniques in the diagnosis of detrusor instability because patients with detrusor instability diagnosed on CMG do not routinely undergo AM.

Early in our use of AM, provocation tests were not routinely incorporated and 2 patients (not reported here) were found to be unstable on provocation during conventional cystometry but were stable during filling on ambulatory monitor-

ing. During AM, therefore, we recommend the use of a protocol which includes time to reproduce those activities that the patient associates with the development of symptoms.

Provocative manoeuvres such as coughing and heel-bouncing had been incorporated into the cystometrogram prior to the original description of detrusor instability as a cause of urgency and incontinence (Hodgkinson *et al.*, 1963; Bates, 1971). Further provocation tests which have been tried in an attempt to improve diagnostic yield have included the use of fast filling rates, low temperature fluids and Foley catheters with the balloon inflated; these led to an unresolved debate on the relevance of unstable contractions diagnosed by such methods (Ramsden *et al.*, 1977).

It seems that a method of recording that interferes as little as possible with normal activities should produce the most clinically relevant information. The use of natural filling cystometry in the diagnosis of detrusor instability has been reported previously (James, 1978, 1983; Fantl, 1984), but in these studies no direct comparison with conventional urodynamic studies was available and the recording systems were not completely ambulatory because the patients were connected to a fixed recording apparatus via trailing wires. James (1978, 1983) stressed the importance of the increased mobility and increased time for study which are available during natural bladder filling cystometry and which allow a more realistic reproduction of the provocative manoeuvres met by the patient in daily life. This conclusion is supported by our findings.

Thüroff *et al.* (1980) investigated the use of natural filling ambulatory monitoring and CMG in 10 young male volunteers. DI was found in 2 (20%) on CMG but in a further 4 (40%) on AM. The present study has confirmed that AM is more sensitive in the detection of phasic detrusor activity. We do not yet know the clinical relevance of such activity. However, the finding that such activity was associated with symptoms and urinary leakage in 15/31 patients with instability diagnosed on AM suggests that at least in some patients such activity may be of clinical importance.

A conventional urodynamic test is quick and convenient for both clinician and patient but a normal result does not exclude the diagnosis of detrusor instability. We have found that ambulatory monitoring is useful in the diagnosis of both genuine stress incontinence and detrusor instability in patients with a strong clinical history of incontinence and in whom no abnormality was found on CMG.

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Problems in the Surgical Treatment of Interstitial Cystitis

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Summary—Two series of patients with histologically proven interstitial cystitis that was unresponsive to hydrostatic bladder distension and intravesical chemotherapy with dimethyl sulfoxide have been studied. In the first series 24 patients were treated by subtotal cystectomy and substitution cystoplasty without further consideration; 8 of these 24 patients had persistent frequency due to active disease in the remaining trigone and/or urethra and in 2 cases this was severe.

Because of this experience the second group of patients had routine biopsy of the trigone and assessment of urethral sensation as part of the initial assessment. In those in whom the trigone was unaffected, treatment was unchanged. If the trigone was affected, total cystourethrectomy was performed with substitution cystourethroplasty unless the patient chose or was advised to avoid surgery altogether or to have a simpler option such as conduit or continent urinary diversion.

Trigonal biopsies should be part of the routine assessment of all patients being considered for surgery, since residual active disease is a major cause of dissatisfaction after subtotal cystectomy and substitution cystoplasty.

When a patient with interstitial cystitis fails to respond to non-surgical treatment and is fit for surgery, subtotal cystectomy and substitution cystoplasty are usually considered. The results of this procedure are generally good, particularly in the “classical” form of interstitial cystitis with “Hunner’s ulcer” affecting the dome of the bladder but sparing the bladder base. With the more diffuse type of interstitial cystitis, which seems to be more commonly recognised now than previously, the results are less satisfactory.

This report describes our experience of the surgical treatment of interstitial cystitis in a consecutive series of 49 female patients.

Patients and Methods

A group of 49 adult female patients aged 36 to 73 years were considered for surgery. All had histologically proven interstitial cystitis according to generally accepted criteria. All had initially been treated by hydrostatic bladder distension on at least

1 occasion and with intravesical dimethyl sulfoxide at least. All had failed to respond to these methods and all considered their symptoms to be sufficiently severe to warrant major surgery.

The first 24 patients (prior to 1984) were treated by subtotal cystectomy and substitution cystoplasty. In the subtotal cystectomy all of the bladder above the level of the ureteric orifices posteriorly and the bladder neck anteriorly was removed and only the trigone below the level of the ureteric orifices was retained. The results of surgery in these patients were less than ideal because 8 patients had persistent frequency and urgency and biopsy of the trigonal remnant showed active disease. In 2 cases this was particularly severe and required excision of the remaining trigone and urethra with substitution urethroplasty to resolve the problem. Since 1984, therefore, the trigone has been biopsied routinely and urethral sensitivity to catheterisation has been noted as a means of assessing whether excision of the entire lower urinary tract is required in order to eliminate symptoms. Patients with a positive trigonal biopsy and urethral hypersensitivity were offered cystourethrectomy with substitution cystourethroplasty (Mundy, 1988); alternatively, it was suggested that either they

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tolerate their symptoms or consider a diversion (continent or conduit) as a lesser procedure. If the trigone and urethra appeared free of disease, then subtotal cystectomy and substitution cystoplasty were performed as before, assuming that they too did not wish to tolerate their symptoms or consider a diversion.

Results

Of the 25 patients who had routine biopsy of the trigone as part of the initial assessment, 13 had active disease in the trigonal remnant and 12 appeared disease-free. The 12 who were disease-free underwent cystectomy and substitution cystoplasty; in 10 cases the results were entirely satisfactory but 2 patients still had symptoms of persistent frequency and urgency for which no cause could be found.

Of the 13 patients with positive trigonal biopsies, 8 underwent total cystourethrectomy and substitution cystourethroplasty. One of these patients has stress incontinence but does not find it intolerable. Of the remaining 5, 2 chose to live with their symptoms, 2 underwent continent diversion with a Mitrofanoff type of procedure and 1 underwent conduit diversion. All 5 patients were advised against major reconstructive surgery because of the scale of the surgery in relation to their physical fitness and their expectations.

Discussion

The pattern of interstitial cystitis seems to have changed in the last 20 years, although there is no documented evidence of this. Whether or not the more diffuse types of "mast cell cystitis" now grouped within the general category of interstitial cystitis are a new phenomenon or simply previously unrecognised as such is not clear, but 20 years ago such patients were not considered for subtotal cystectomy and substitution cystoplasty. The only ones who were considered were those with classical "Hunner's ulcer" and the results in these patients were tolerably good if hydrostatic bladder distension failed to help. This still seems to be the case, although the incidence of sphincter weakness incontinence in association with interstitial cystitis is surprisingly high (Nurse *et al.*, 1988), albeit rarely a cause for complaint.

Subtotal cystectomy and substitution cystoplasty is a major procedure but nonetheless straightforward, and most patients have a predictable outcome. Cystourethrectomy is a much bigger procedure than subtotal cystectomy and substitu-

tion cystourethroplasty, with the need to create a "sphincter mechanism", is more uncertain in its outcome than substitution cystoplasty alone. This poses problems in 2 ways. Firstly, not all patients who are fit enough for the simpler procedure will be fit enough for the more complicated procedure and there is an increased likelihood with the latter procedure of post-operative problems due to failure of the surgically created "sphincter mechanism". Secondly, some patients will not wish to undergo a major operation on this scale with the possibility that they may require a revision procedure later on. It is therefore important to know by trigonal biopsy whether or not subtotal cystectomy and substitution cystoplasty will be adequate on their own or likely to be followed by persistent symptoms, and patients in this group will need to be reselected as to whether they are fit enough or motivated for the major procedure of cystourethrectomy and substitution cystourethroplasty or whether they would be better off considering an alternative.

There has been considerable debate in recent years on the question of detubularisation of gut segments used in substitution cystoplasty. Our own experience (Nurse *et al.*, 1988) is that this is unnecessary if the sphincter mechanism is normally innervated and is functioning normally. Furthermore, patients with "straight" cystoplasties void without difficulty but those with detubularised cystoplasties usually have to catheterise and this could be a major, if not insuperable, disadvantage in patients with interstitial cystitis because of their increased urethral sensitivity. We therefore chose to perform a "straight" cystoplasty if the natural bladder outflow was retained.

In conclusion, we consider that trigonal biopsy and assessment of urethral sensitivity should be a routine part of the pre-operative assessment of patients with interstitial cystitis who are being considered for surgery.

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Conservative Treatment of Vesicovaginal Fistulas by Bladder Drainage Alone

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Summary—We describe 4 cases of conservative management of vesicovaginal fistulas occurring as a complication of abdominal and vaginal hysterectomy. In all cases treatment involved simple bladder drainage for periods ranging from 19 to 54 days. At follow-up all patients remained dry. Such spontaneous closure of vesicovaginal fistulas following adequate bladder drainage has not been previously reported.

The first historical indication of the occurrence of vesicovaginal fistulas (VVF) comes from the examination of old Egyptian mummies as described by Avicenna (10th century). VVFs were regarded as incurable until Sims reported successful results in 1852 (Tahzie, 1983). Since then there have been considerable developments in the technical approach to this condition. Spontaneous closure has been described in individual case reports (Goulinea *et al.*, 1985).

In the African continent the most important aetiological factors are obstructed labour (84%) and "gishiri cutting" (13%); the latter is common practice in eastern Africa and involves cutting the anterior wall of the vagina with a sharp object to prevent obstructive labour, *etc.* In the western world, VVFs occur following gynaecological surgery (82%), obstructed labour (8%) and radiotherapy (6%) (Lee *et al.*, 1988). A small percentage of fistulas are due to malignancy, foreign bodies, injury and sexual intercourse (Sharma *et al.*, 1987). Until now, surgical correction has been the treatment of choice. We describe a simple method of conservative management with an indwelling catheter that is suitable for all fistulas of gynaecological origin providing they are discovered early, before epithelialisation has taken place.

Patients and Methods

In 4 patients aged 41 to 48 years a VVF occurred

after gynaecological surgery. Two patients underwent an abdominal and 2 a vaginal hysterectomy for benign conditions.

Case Reports

Case 1. A 48-year-old woman underwent a vaginal hysterectomy for intermenstrual blood loss. During the operation the bladder and right ureter were injured. Immediate repair was performed by a urologist. The ureter was reimplanted and stented with a double pigtail catheter. The bladder wound was closed using 2/0 vicryl sutures and an 18 F suprapubic Malecot catheter was inserted. Twelve days later the catheter was removed and the patient noticed marked urinary loss *per vaginam*. Instillation of methylene blue and cystoscopy confirmed the existence of a VVF on the right side of the bladder base. An indwelling 20 F urethral catheter was left in place for 42 days. For the first 28 days light suction drainage of 10 cm H₂O was applied to the catheter. Following this treatment the patient has remained dry.

Case 2. A 41-year-old woman underwent a vaginal hysterectomy for prolapse of the uterus. Leakage of urine *per vaginam* became apparent 10 days post-operatively. At cystoscopy a VVF was seen and an 18 F suprapubic catheter was inserted for 26 days. During the first 12 days suction drainage of 10 cm H₂O was applied to the catheter. With this treatment the patient became continent.

Case 3. A 45-year-old woman underwent an abdominal hysterectomy because of excessive intermenstrual bleeding. The bladder was inadvertently opened on 2 occasions during the operation and was immediately repaired. Post-operatively an indwelling urethral catheter remained *in situ* for 11 days. Upon removal of the catheter

urinary leakage *per vaginam* became apparent. Instillation of methylene blue and cystoscopy confirmed the presence of a VVF. The bladder was drained with a 20 F indwelling urethral catheter for 36 days. The patient remained dry upon removal of the catheter.

Case 4. A 45-year-old woman underwent an abdominal hysterectomy for uterine myomatosis. Ten days post-operatively urinary leakage *per vaginam* became apparent. At cystoscopy a VVF was discovered and an indwelling urethral catheter was inserted for 7 days. One month after discharge she returned with recurrent urinary loss *per vaginam*. The bladder was drained for a further 12 days with successful results.

All patients were treated with anticholinergic medication and with antibiotics; urine cultures were made regularly.

Discussion

Most VVFs are complications of gynaecological surgery. It is clear that recognised intra-operative urological complications should be repaired immediately. Although good results can be achieved with early surgery (Badenoch *et al.*, 1987; Cruikshank, 1988), most urologists prefer delayed surgical repair approximately 8 to 12 weeks following the primary surgery.

In 2 patients we applied light suction drainage but despite an indwelling catheter, vaginal urinary leakage persisted. In our 4 patients the VVFs closed spontaneously following conservative management. This closure occurred within 8 weeks after hysterectomy. The drainage times ranged from 19

to 54 days and all patients were continent at follow-up 1 to 14 years later. The treatment was well tolerated and there were no complications.

We do not suggest that all patients whose gynaecological surgery is complicated by a VVF will be successfully managed by this conservative technique. We have treated only 4 patients but all have remained dry on follow-up. In cases where delayed repair of a VVF is planned primarily, or following failure of early repair, further surgery may be avoided by using this simple conservative technique.

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Cystoscopic Suction Diathermy for the Treatment of Superficial Bladder Tumours

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Summary—The treatment of superficial bladder tumours (Ta, T1) is a time-consuming exercise for urological surgeons and patients. A method of treating the tumours, whether primary or recurrent, by endoscopic suction diathermy has been developed. The technique significantly reduces the amount of tumour debris within the bladder during treatment as well as the amount of diathermy employed. By removing the free tumour cells in the irrigation fluid the risk of tumour cell implantation may be kept to a minimum.

A review of patients in this unit a few years ago suggested that those treated by open excision of large superficial bladder tumours experienced a longer disease-free interval than others treated by transurethral resection (TUR). This led to an examination of the 16 patients with superficial tumours treated by open excision between 1962 and 1973. Of the 16 patients examined retrospectively 11 were recurrence-free at 4 years and 5 had had 1 or more recurrences, a recurrence rate of 31%. In the light of these results a retrospective comparison was made with a further group of patients treated by TUR and matched for age and sex as well as size and number (1–3) of initial tumours, including stage and histological grade. In this group of 16 patients only 2 were recurrence-free at 4 years, a recurrence rate of 87% (Tables 1 and 2).

A comparison of the 2 procedures, open excision and TUR, suggested that the early isolation of tumour tissue in the open operation, combined with the removal of the more friable portions of tumour by direct suction and copious irrigation, may have led to a reduction in the recurrence rate due to implantation. Moreover, it was felt that the most important factor lay in the immediate application of suction to the tumour to remove its more friable

portions in the open technique, thereby reducing the free tumour cell density. The idea of removing bladder tumours by suction is not a new one. The technique was routinely employed many years ago as a means of debulking large tumours, albeit blindly, by attaching a suction syringe to the end of the cystoscope sheath after positioning under vision (Burnside, 1972). This approach has now been refined to allow simultaneous suction and diathermy of tumours under direct visual control.

The aim of this technique is 2-fold: firstly, to reduce the tumour cell emulsion produced at the time of resection of the tumour and hence reduce the free tumour cell density; secondly, to reduce the amount of bladder urothelial damage, as caused by diathermy heat and evacuation, to a minimum.

Patients and Methods

An initial trial of the technique was carried out with the aid of a bronchial suction catheter passed down the instrument channel of a standard cystoscope. The surface of superficial tumours was found to be friable enough to be removed by suction alone. Subsequently a 9 F flexible suction diathermy tube has been designed which allows simultaneous use of controlled suction and diathermy. This can be passed down the instrument channel of a standard 23.5 F cystoscope. A suction diathermy resectoscope similar to the loop resectoscope used

Table 1 Open Operation *vs* Transurethral Resection. Details of Patients

	<i>Open operation (16) Suprapubic diathermy excision (14) Partial cystectomy (2)</i>	<i>Transurethral resection (16)</i>
Age (years)	35–74 (mean 59.3)	35–72 (mean 58.7)
Sex (Male: female)	13:3	13:3
Size of tumour (cm)	2–4	2–4
Histology		
Grade I TCC	6	7
Grade I–II TCC	6	7
Grade II–III TCC	4	2
Follow-up (years)	Minimum 4	Minimum 4

TCC = Transitional cell carcinoma.

Table 2 Results at 4 Years

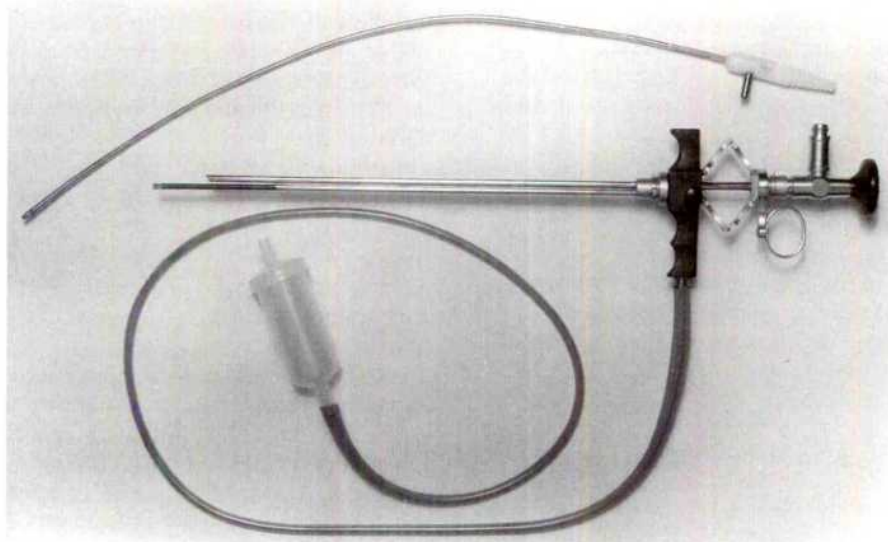
<i>Group</i>	<i>No of patients</i>	<i>No. of tumours</i>	<i>No. of tumour episodes</i>
Open surgery	16	12	8
Tur	16	117	54

for transurethral resection of the prostate (TURP) has also been developed which has a larger diameter rigid suction tube with a terminal diathermy ring (Fig.).

The suction tube is connected to standard theatre suction apparatus via a filter for collection of the tumour portions thus removed and incorporates a

finger plate to allow instant and accurate variation in suction strength and duration. The tumour base may be resected using a conventional resectoscope to confirm the superficial nature of the lesion if necessary.

Superficial tumours found on check cystoscopy of patients with recurrent Ta, T1 disease and on

**Fig.** Flexible suction diathermy tube (above) and rigid suction diathermy resectoscope with attached filter (below).

new patients undergoing cystoscopy for haematuria were treated with suction diathermy when an instrument was available. Aliquots of irrigating fluid were collected per-operatively and the tumour cell density estimated by direct microscopy of the specimens. Follow-up cystoscopies were performed after 3 months.

Prototype suction diathermy tubes have now been employed on over 40 occasions with ease and without complication. The technique has been used in females with small tumours under local anaesthesia with minimal discomfort.

Results

Seventeen patients with superficial tumours treated solely by suction diathermy, when a suitable instrument was available, were followed up. The results show a reduction in recurrences following suction diathermy, 88% (15/17) having fewer tumours after suction diathermy, whereas only 33% (5/15) of the patients with tumour on the first recorded cystoscopy had a decrease in number following standard diathermy methods (Table 3). The technique is easy to learn, certainly no more difficult than the standard methods presently employed and, with experience, is probably quicker than present methods of eliminating tumours. The bulk of a superficial tumour is friable enough to be

removed by direct suction alone and diathermy need only be employed to free more adherent portions of tumour, secure haemostasis and to fulgarise or resect the tumour base. There is a greatly reduced free tumour cell density in aliquots of irrigating fluid removed per-operatively. In fact, on examining the fluid by microscopy, no tumour cells were seen in the fluid removed during suction diathermy. This compares very favourably with the figures quoted by See and Chapman (1987) for free viable tumour cells released at the time of resection by both laser and standard electrocautery.

At the time of resection with suction diathermy the operative field is clearer than that seen during the standard techniques since there is no tumour emulsion and blood is immediately removed from view. Tumours do not explode, as is frequently seen using diathermy alone, and this significantly reduces tumour debris scatter in the bladder. The gas bubble at the vault may also be extracted by suction, allowing better visualisation and treatment in this area. Tumours in difficult access areas, especially around the bladder neck, can be sucked into view prior to diathermy. The specimens collected in the on-line filter during tumour treatment are at least comparable with those obtained by the standard methods. The closed system of bladder emptying and tissue collection significantly decreases the danger of operator contamination which may occur during the standard biopsy and bladder washout procedures.

Table 3 Suction Diathermy Treatment of Superficial Bladder Tumours

Patient no.	No. of superficial tumours present at cystoscopy		
	≥ 3 months prior to SD*	at SD	≥ 3 Months after SD
1	New patient	1	Nil
2	5	2	1
3	8	> 10	Nil
4	Nil	1	Nil
5	5	> 10	1
6	8	> 10	1
7	4	> 10	2
8	Nil	1	Nil
9	New patient	4	Nil
10	1	1	Nil
11	2	3	Nil
12	1	> 10	> 10
13	> 10	4	Nil
14	> 10	1	3
15	3	1	Nil
16	5	> 10	2
17	> 10	> 10	6

* = Suction diathermy.

Discussion

A review of the literature suggests that more than 70% of all bladder tumours are superficial (Ta, T1). Even after complete TUR of all visible lesions, up to 60% recur (Pyrah *et al.*, 1964; Barnes *et al.*, 1967; Heney *et al.*, 1982). Although intravesical chemotherapy may reduce the recurrence rate it is time-consuming, costly and may be unpleasant for the patient.

Two explanations have been put forward to account for the high recurrence rates of superficial bladder tumours;

(1) *The multicentric theory.* Proposed initially by Hansemann in 1890, direct experimental evidence supporting this theory was provided by the work of Kaplan and others in 1951.

(2) *The tumour cell implantation theory.* This mechanism was proposed originally by Albarran and Imbert in 1903 and has been supported by

others (Wallace, 1973; Williams *et al.*, 1977; Smith, 1981). Hinman (1956) reported 3 cases of tumour recurrence at the bladder neck when it had been resected for obstructive symptoms at the same time as a tumour. It was proposed that mucosal damage was an important factor in the implantation of tumour cells, suggesting also that vigorous and extensive use of evacuators during resection may cause trauma to bladder mucosa, which could be a further source of recurrence.

Evidence in support of the implantation theory was provided by Boyd and Burnand in 1974. In a small prospective study of 32 patients with superficial bladder tumours treated by standard transurethral techniques, it was found that only 3% of primary tumours occurred on the vault, although 90% of all patients had a vault recurrence at some stage; indeed, in 19% of the patients the vault was the only site of recurrence. It was suggested that tumours recurring at 3 months were more likely to be due to implantation, whereas those recurring after a disease-free interval of many years were probably not due to this mechanism. It was observed also that, during the resection of the tumours, clumps of tumour cells, some of which were presumably viable, could be seen adhering, by surface tension, to the gas bubbles released at diathermy. The bubbles then rose to the vault, carrying with them the tumour cells which could subsequently implant, possibly into areas where the mucosal integrity had been breached.

It has been suggested that an increase in mucosal damage in the vault area may occur indirectly as a result of cystodiathermy. Blandy (1978) has shown that the temperature at the tip of the diathermy electrode reaches 1000°C during transurethral resection. The gases released at diathermy have been analysed and been found to consist largely of hydrogen, hydrocarbon and carbon monoxide, which may be harmful to the mucosal barrier (Davis, 1983). Undoubtedly, the diathermy gases can be seen to accumulate as a gas bubble at the vault during transurethral procedures and may be expected to cause increased mucosal damage because of toxic and burn effects.

Implantation of tumour cells has been shown to occur in dogs by McDonald and Thorson (1956). Soloway and Masters (1980) supplied supportive evidence by inoculating free bladder tumour cells into normal and cystodiathermy-damaged bladders of mice. An implantation rate of 12% was shown in mice with normal bladders compared with a rate of 54% in mice whose bladders had been damaged by cystodiathermy. Implantation in the mouse model

may be significantly reduced by intravesical instillation of thiotepa. However, it had to be instilled into the diathermy-damaged bladder within an hour of the inoculation of tumour cells (Pan *et al.*, 1989). This suggests that implantation occurs rapidly after the initial endoscopic treatment of tumours and the thiotepa may act by preventing tumour cell adherence to areas of urothelial damage.

Differing recurrence rates have been noted when comparing the use of the YAG laser with the standard electrosurgical techniques. The animal models of See and Chapman (1987) showed that cystodiathermy produced 620% more viable free tumour cells than the YAG laser during tumour ablation and it was concluded that the decreased inoculum size with laser treatment was responsible for the observed decrease in recurrence rates in some reported series.

The 2 factors, therefore, which may be important in the recurrence of superficial bladder tumours due to implantation are bladder urothelial damage and volume of inoculum of viable tumour cells.

Suction diathermy promises to be a safe and easy procedure for the treatment of superficial bladder tumours. By decreasing the floating tissue debris and removing the gas bubble at the vault, visualisation throughout the treatment is greatly improved. There is a substantial reduction in the amount of free tumour cells present within the bladder at the time of resection and the amount of diathermy required is decreased. The expectation is that by reducing both the free tumour cell density and the mucosal damage produced at the time of resection, recurrences due to implantation will be minimised.

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Flexible suction diathermy tubes and specimen filters are available through Euro Surgical Ltd, The Common, Cranleigh GU6 8LU.

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Results of Medical Research Council Phase II Study of Low Dose Cisplatin and Methotrexate in the Primary Treatment of Locally Advanced (T3 and T4) Transitional Cell Carcinoma of the Bladder

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Summary—A series of 49 previously untreated patients with category T3 or T4 bladder cancer underwent treatment with low dose methotrexate and cisplatin; 44 patients were eligible for assessment of response. Complete response (CR) was seen in 5 patients (11%) and partial response in 15 (34%) (overall response rate 45%). Treatment was reasonably well tolerated with no major morbidity and no treatment-related deaths.

After a median follow-up of 3.5 years, the 1-year and 2-year survival rates were 70 and 30% respectively. Ten patients remain recurrence-free without having received "definitive local therapy" (cystectomy and/or radiotherapy) at follow-up extending from 20 to 50 months.

Transitional cell carcinoma of the bladder which invades either the bladder wall muscle or the prostate, or vagina, or which has spread beyond the bladder to the deep pelvis (category T3 and T4) (UICC, 1978) carries a poor prognosis. Treated conventionally (with total cystectomy, radiotherapy or a combination of these modalities), only 30 to 40% of patients with T3 bladder cancer (Goffinet *et al.*, 1975; Wallace and Bloom, 1976; Mather *et al.*, 1981; Bloom *et al.*, 1982; Skinner and Lieskovsky, 1984; Shipley *et al.*, 1985) and 10% of those with T4 tumours will survive 5 years (Goffinet *et al.*, 1975; Blandy *et al.*, 1980; Goodman *et al.*, 1981; Shipley *et al.*, 1985). Typically, 40 to 50% will survive 2 years (Finney, 1965; Duncan and Quilty, 1986). These disappointing survival rates for T3 bladder cancer are achieved at the cost of considerable morbidity (Goffinet *et al.*, 1975). In the majority of patients with locally advanced bladder

cancer, treatment has palliative aims, mainly with the object of reducing haematuria and the subjective symptoms of dysuria and increased urinary frequency. The fact that some patients with advanced bladder cancer have achieved the relief of such symptoms with the use of cytotoxic drug combinations has increased the interest in the role of chemotherapy in the primary management of locally advanced bladder cancer. Initial studies have described single-agent response rates in the bladder with cisplatin (Fagg *et al.*, 1984; Raghavan *et al.*, 1984; Raghavan, 1987) and methotrexate (Oliver, 1981) of 20 to 40%. The aim of this study was to examine the potential effect of a combination of low dose cisplatin and methotrexate on the response of the primary bladder tumour, as a prelude to randomised trials.

Patients and Methods

The study group comprised patients presenting between August 1984 and January 1987 with previously untreated transitional cell carcinoma of the bladder, categorised according to TNM criteria

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as T3a, T3b, T4a or T4B, NX, MO or M1 (UICC, 1978). In accordance with this earlier UICC staging system, the results of bimanual examination were incorporated into the tumour categorisation. Previous endoscopic resections or intravesical chemotherapy for superficial bladder cancer were not exclusion criteria. All eligible patients were of WHO performance status 0, 1 or 2 with initial serum creatinine $< 120 \mu\text{mol/l}$, creatinine clearance $> 60 \text{ ml/min}$, initial white blood count $> 3.5 \times 10^9/\text{l}$ and platelet count $> 120 \times 10^9/\text{l}$.

Chemotherapy was given as follows. On Day 1 a litre of normal saline was given intravenously over 3 h, followed by methotrexate 40 mg/m^2 given as an intravenous bolus. This was immediately followed by cisplatin 70 mg/m^2 , given as a 3-h intravenous infusion in 500 ml normal saline, followed by a further 3 l normal saline, each containing 20 mEq KCL over 24 h. A further dose of methotrexate 40 mg/m^2 was given, as an intravenous bolus, on Day 15. The treatment was repeated every 28 days for a total of 3 cycles, after which therapy was at the discretion of the responsible physician.

Modifications were made to treatment in accordance with the following rules. On Day 15, if the white blood count was less than $3.0 \times 10^9/\text{l}$ or platelet count $< 100 \times 10^9/\text{l}$, the methotrexate bolus was omitted. Similarly, if on Day 28 the white blood count was less than $3.0 \times 10^9/\text{l}$ or platelet count $< 100 \times 10^9/\text{l}$, treatment was deferred until these values had returned to normal up to a maximum of 2 weeks. If recovery of blood count was not complete within 2 weeks the patient was excluded from the study.

If on Day 15 the serum creatinine exceeded $120 \mu\text{mol/l}$, methotrexate was omitted. If on Day 28 the serum creatinine exceeded $120 \mu\text{mol/l}$, treatment was deferred until it fell below this level or until the creatinine clearance exceeded 80 ml/min .

Assessment of tumour

Prior to chemotherapy, the primary bladder tumour was assessed by cystoscopy, transurethral resection biopsy (TURB), bimanual examination under anaesthesia (EUA) and CT scan of the pelvis with 1-cm cuts through the tumour. Complete endoscopic resection of the tumour was not attempted and it was left in the bladder to serve as a marker of response to therapy. Patients were assessed for response at 12 weeks and 5 months after entry, irrespective of the number of cycles of chemotherapy they received. Assessments were made by

cystoscopy, bimanual examination under anaesthesia, TURB and CT scan of the pelvis. CT scan was repeated at 6 months if pelvic surgery or radiotherapy had not been carried out. Cystoscopy and bimanual examination under anaesthesia were also repeated at 6 months with TURB of any residual or recurrent tumour. The response assessment included patients who received only a single cycle of chemotherapy.

Complete remission was defined as the complete disappearance, on a single observation at the end of treatment, of all clinical, radiological and histological evidence of malignant disease in the bladder or pelvis or distant metastases. Partial remission was defined as at least 50% reduction in the product of the 2 largest diameters of the bladder tumour mass. No change was defined as a change of less than 50% reduction or less than 25% increase in the product of the 2 largest perpendicular diameters of the bladder tumour mass. Progressive disease was defined as an increase of more than 25% in the product of the 2 largest perpendicular diameters of the bladder tumour mass. At the start of the study the problems of assessing radiological, bimanual and cystoscopic serial sizes of a tumour of a complex 3-dimensional shape related to a distensible organ of variable volume were not appreciated. Where a discrepancy existed between the clinical assessment of tumour response at EUA and/or cystoscopy and the CT scan assessment, the "worst case" was taken for the purpose of analysis of the results. For example, if on EUA and cystoscopy no evidence of tumour was found but the CT scan demonstrated residual mass, the response was assessed as a partial remission (see Discussion).

Review of pathology

All material was reviewed and the presence of transitional cell carcinoma confirmed (by M.C.R.). Post-treatment biopsies, where available, were also reviewed to confirm the presence or absence of tumour. These were employed mainly as a quality control check. Patients with positive post-treatment biopsies were regarded as non-responders, or partial responders if the appropriate reduction in size had occurred.

Symptomatic response and assessment of toxicity

To assess the palliative benefit and symptomatic response, urinary symptoms (frequency of micturition, nocturia, haematuria, dysuria and incontinence) were recorded prior to treatment by the responsible physician and at the time of tumour

assessment, on an individual basis. Complete response was defined as complete absence of urinary symptoms after chemotherapy, improvement as a disappearance of 1 or more urinary symptoms and no worsening of existing symptoms. The WHO criteria for haematological toxicity were employed.

Results

A total of 49 patients entered the study from 7 centres (Table 1). Details of patients at entry to the trial are presented in Table 2. Their ages ranged from 37 to 78 years (mean 66).

Five patients were deemed ineligible. One had received prior radiotherapy to the pelvis and had an initial creatinine clearance <60 ml/min; 2 patients had an initial serum creatinine >120 μ mol/l and another patient had no measurable disease following TURB. The fifth patient had an adenocarcinoma of the prostate.

Table 1 Entry by Institution

Hospital	No. of patients entered
Freeman, Newcastle upon Tyne	16
Newcastle General, Newcastle upon Tyne	1
Norwegian Radium, Oslo	19
Royal Marsden, Sutton	1
Western General, Edinburgh	4
York District, York	6
Princess Royal, Hull	2
Total	49

Table 2 Details of Patients at Entry to the Trial

Characteristic	No. of patients
Sex—Male	38
Female	11
Category—T3–T4a	26
T4b	23
Clinical metastases—Present	6
Absent	43

Response of tumour

The main end point of this study was the response of tumour at 12 weeks. The overall response rate was 45% (95% confidence interval, CI 31 to 60%), with 5 patients (11%) achieving a complete response and 15 (34%) achieving a partial response of the primary tumour (Table 3); 16 of the 20 12-week responders (80%) maintained their response to 6

Table 3 Response of Primary Tumour at 12 Weeks

	No. of patients (%)
Complete response	5 (11)
Partial response	15 (34)
No change	14 (32)
Progression	9 (20)
Not done	1 (2)
Total	44

months. The local definitive treatment received by response at 12 weeks is set out in Table 4. One patient was not formally assessed for response at 12 weeks.

A total of 9 patients who had achieved partial or complete remission received either no further therapy or further cycles of chemotherapy; 1 of these 9 patients died of acute myeloid leukaemia at 15 months with no sign of activity of his bladder carcinoma. The remaining 8 patients were alive and well, at last follow-up, with no sign of activity of their bladder cancer.

A further 2 patients whose tumours failed to respond to chemotherapy and were locally resected (in 1 case by "radical transurethral resection of tumour" and in the other by partial cystectomy) were each given 2 further cycles of chemotherapy and remain alive and well more than 4 years after entry to the study.

Survival

After a median follow-up of 3.5 years, 11 patients (25%) are alive. The actuarial survival is presented in the Figure. At 1 and 2 years the actuarial survival was 70 and 30% respectively. Most deaths have been due to bladder cancer, although 2 patients have died from other diseases: 1 died of septicaemia following a cystectomy and the other died of acute myeloblastic leukaemia.

Response of symptoms

Only 1 patient in the study had no initial bladder symptoms. At second assessment, 32 patients (74%) had a response of urinary symptoms after chemotherapy (Table 5). No urinary symptoms were worse at this point.

All patients whose tumours responded completely on clinical and radiological assessment had improvement in their urinary symptoms, as did 12 of the 15 partial responders. It is of interest that in 15 patients whose tumours were static or progressed during treatment, there was an improvement in urinary symptoms, with complete resolution of these symptoms in 7.

Table 4 Further Treatment Received by Response at 12 Weeks

Treatment	Response at 12 weeks					Total
	Complete	Partial	No change	Progression	Not assessed	
None	0	4	2	4	1	11
Radiotherapy	3	4	7	3	0	17
Cystectomy	0	1	0	1	0	2
Chemotherapy	2	4	1	0	0	7
Radiotherapy and cystectomy	0	0	1	0	0	1
Radiotherapy and chemotherapy	0	1	1	1	0	3
Cystectomy and chemotherapy	0	1	3	0	0	4
Total	5	15	14	9	1	44

Fourteen of the 32 patients (44%) who responded symptomatically at 12 weeks had a continued response at 6 months, having received either additional chemotherapy or no further treatment.

Toxicity

The reasons for not receiving 3 cycles of chemotherapy are outlined in Table 6; 6 patients refused further treatment, 2 experienced tumour progression and 1 suffered excessive renal toxicity. In all, 35 patients received 3 cycles of chemotherapy, 5 received 2 cycles and 4 received 1 cycle.

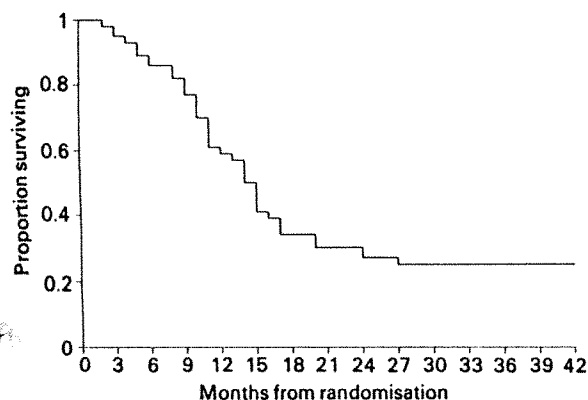
Eleven patients did not receive methotrexate on Day 15 on at least 1 cycle. In 1 case no reason for omission was given. In another the dose was omitted because of rapid disease progression with clinical deterioration. In 4 patients there was a transient elevation of creatinine, accompanied in 1 case by a fall in white blood count. In 2 further cases a low white blood count was responsible for the Day 15 methotrexate being omitted; in 1 of these the fall in white blood count was accompanied by mucositis. In 2 patients a fall in platelet count

Table 5 Response of Bladder Symptoms at 12 Weeks

Response	No. of patients (%)
Complete	18 (41)
Improved	14 (32)
No response	11 (25)
Deteriorated	0 (0)
No initial symptoms	1 (2)
Total	44

Table 6 Reasons for not Receiving 3 Cycles of Chemotherapy

Reason	No. of patients	
	Withdrawn after 1 cycle	Withdrawn after 2 cycles
Patient refused treatment due to severe nausea and vomiting	2	1
Patient refused treatment due to depression	1	1
Tumour progression	1	1
Patient refused treatment due to lethargy and malaise	0	1
Poor renal function	0	1
Total	4	5

**Fig.** Overall survival for all eligible patients.

resulted in omission of the Day 15 methotrexate, but in only 1 case was mucositis alone the reason for omission.

No treatment-related deaths occurred and no major drug toxicities were reported in this study. Gastrointestinal toxicity was not a significant problem (Table 7).

Nausea was recorded as absent or mild in 50% of patients and 39% were recorded as not vomiting at all during treatment. Prophylactic anti-emetic therapy was routinely given, usually with high dose

metoclopramide alone, or in combination with dexamethasone and lorazepam; 70% of patients had no oral mucositis and in only 1 case was it so severe as to interfere with eating.

Table 7 Maximum Drug-related Gastrointestinal Toxicity Observed During Chemotherapy

Toxicity	None (%)	Mild (%)	Moderate (%)	Severe (%)	No. of patients
Nausea	22 (50)		16 (36)	6 (14)	44
Vomiting	17 (39)	15 (34)	9 (7)	3 (7)	44
Mucositis	31 (70)	7 (16)	5 (11)	2 (2)	44

Myelosuppression was not severe, with only 1 patient experiencing WHO grade 3. ($1.9 \times 10^9/l$ WBC count) toxicity. There was no evidence of nadir-related sepsis. Platelet toxicity was reported in only 3 patients, 1 grade 1 and 2 grade 2. No symptomatic episodes of thrombocytopenia were recorded.

During the course of the study 3 patients required blood transfusion. In each case there was progression of primary tumour and, in 2 of the 3, synchronous metastatic progression. It is therefore impossible to attribute their transfusion requirements specifically to either the chemotherapy or to the progressive tumour.

Twenty-two elevations of serum creatinine above the upper limit of normal were observed in 13 patients (30%). The mean maximum serum creatinine measured in these patients was $137 \mu\text{mol/l}$ (range 121–170). In only 4 patients did the serum creatinine not return to normal at the time of completion of, or withdrawal from, chemotherapy. In 1 case the tumour failed to respond to chemotherapy—the patient deteriorated and died of pulmonary embolus after being withdrawn from chemotherapy. In the other 3 patients the serum creatinine subsequently returned to normal. Diarrhoea was reported in 4 patients and lethargy in 2. Two patients with severe depression refused further treatment. Mild skin rash, severe hair loss, “weakness” and weight loss with ankle oedema were each reported in 1 patient. Septicaemia was seen in 1 patient, secondary to a urinary tract infection. This was not associated with neutropenia and resolved with no sequelae.

Discussion

It is difficult to use standard UICC criteria of response when assessing the response of primary bladder carcinomas to chemotherapy. Firstly, as-

essment after treatment is made at a single time point and UICC criteria require 2 assessments at intervals of 4 weeks. Secondly, it has proved difficult to apply the rule of “50% reduction in the product of 2 dimensions at right angles” to a complex, 3-dimensional tumour which relates to the curved wall of a distensible organ of variable volume: further, the apparent volume of “tumour” seen on CT scan may be increased by factors such as blood clot and tissue oedema following transurethral resection of tumour.

Consensus has not been reached on the optimal definition of response (partial or complete) following treatment of bladder tumours and it is perhaps unlikely that the final accepted definition will coincide with that used in this study. Thus patients deemed partial responders in this study, by virtue of persistent CT scan abnormality and/or residual palpable thickening, would be deemed complete responders by others if deep resection biopsies were negative. The definition of partial response to chemotherapy of primary bladder tumours remains a matter of debate, as does the usefulness of the PR category. It may be that the achievement of significant reduction in tumour bulk, however defined, after 2 or 3 cycles of chemotherapy provides evidence of tumour responsiveness.

The overall response rate of 45% accords with what was expected, although the low complete response rate (11%) is somewhat disappointing. It may perhaps be explained by the large initial size of some of the tumours (15 patients had tumours which measured 8 cm or more in at least 1 dimension) or the inclusion of 23 patients with category T4b disease. If response had been assessed after 4 or more cycles, it is possible that some PRs would have been converted to CRs.

At the time this study was instituted there had been reports of the effect of cisplatin and methotrexate on metastatic transitional cell carcinoma (Carmichael *et al.*, 1985) but no reports of the effects of cisplatin-containing combination therapy on the primary tumour. It was therefore left open to individual clinicians to decide on treatment after 3 cycles of chemotherapy. The 10 patients (23% of those eligible for assessment of response) who are alive and well at follow-up intervals of 20 to 50 months (mean 35.6) without total cystectomy or radiotherapy for muscle-invasive bladder cancer are worthy of comment. This unexpected result reinforces the opinion that bladder cancer is a chemosensitive disease in a proportion of patients and provides encouragement for further studies in which initial chemotherapy is employed.

It is also of interest that 32 of the eligible patients (74%) had an improvement in their urinary symptoms during chemotherapy, with 18 (41%) experiencing a complete resolution of these symptoms. This observation is of importance in view of the number of proposed studies of neoadjuvant chemotherapy for transitional cell carcinoma of the bladder, since patients receiving initial chemotherapy are unlikely to be denied prompt and effective palliation of symptoms.

Although no treatment-related deaths and no major life-threatening drug-related toxicities were reported, the regime was not without morbidity, as indicated by the 6 patients who refused further treatment. It is somewhat surprising that, in an elderly population, a cisplatin-containing chemotherapy regimen apparently produced no emesis in 39% of patients and no, or only mild, nausea in 50%. This may indicate that effective anti-emetic regimes were used by a number of investigators, but it is also possible that such events were under-reported.

We have confirmed the activity and the relative lack of toxicity of this combination of cisplatin and methotrexate. Further work is necessary to improve chemotherapy regimes for transitional cell carcinoma, combining worthwhile anti-tumour activity with a level of toxicity that is acceptable to this (often elderly) population. Research is also necessary to define the role of such chemotherapy regimes in the overall management of patients with advanced bladder cancer.

Recent reports, in which other agents (vinblastine with, or without doxorubicin) are added to methotrexate and cisplatin, indicate high response rates in the bladder (Meyers *et al.*, 1985; Scher *et al.*, 1988), although response criteria vary. The low observed complete response rate does not make this an attractive potential regime for neoadjuvant studies, although the durable complete remissions in patients treated only with chemotherapy, or with the addition of only local resection, provide encouragement in that direction.

The Medical Research Council Working Party on Advanced Bladder Cancer has recently conducted a Phase 2 study of the combination of cisplatin, methotrexate and vinblastine and is to embark on a randomised Phase 3 study of this combination prior to definitive radical treatment.

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The Value of Ultrasound Scanning of the Upper Urinary Tract in Patients with Bladder Outlet Obstruction

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Summary—Ultrasound scanning of the upper urinary tract enables a urologist to allocate a degree of urgency for surgery when upper tract dilatation is present. We have studied whether other assessments of bladder outlet obstruction could eliminate this investigation. The study group comprised 223 consecutive patients who had ultrasound scans for bladder outlet obstruction. Estimation of urea, creatinine, residual urine and flow rate could not predict the presence of upper tract dilatation and it was concluded that ultrasound scanning of the upper tracts should continue to be used as a means of deciding how urgently a patient requires prostatic surgery.

Few countries can provide immediate treatment for a patient who requires a prostatectomy. Any delay leads to investigations so that patients can be allocated to an appropriate waiting list category: emergency, urgent, soon, routine, *etc.* The estimation of residual urine by means of ultrasonography and flowmetric analysis have been recommended as an objective measure of bladder outflow obstruction (Abrams, 1977). Other authors rely on symptoms (Frimodt-Moller *et al.*, 1984), but this method produces large numbers of patients who require further investigation before allocating a degree of urgency regarding prostatectomy—hence the use of ultrasonography of the upper tracts for evidence of dilatation, and estimation of the plasma urea and creatinine for evidence of renal failure due to bladder outlet obstruction. Associated upper tract abnormalities have also been noted in this study. It is generally accepted that imaging of the upper tracts to ascertain unexpected pathology is not justified (Talner, 1986; O'Reilly, 1987; Brooks, 1988).

The aim of this study was to assess whether ultrasonography of the upper tracts could be dispensed with if other estimations of bladder outlet obstruction (residual urine and flowmetry) were

known and the serum urea and creatinine results were available.

Patients and Methods

Patients undergoing ultrasound scanning under the care of one urologist (J.A.K.W.) during 1987 and 1988 were evaluated; 373 scans were carried out. Patients who had undergone previous surgery to the lower or upper urinary tract were excluded, as were those with symptoms of loin pain, haematuria, recurrent urinary tract infections and acute retention, together with patients under the age of 50 years. In all, 223 consecutive patients presenting *de novo* with lower urinary tract symptoms suggestive of bladder outlet obstruction were evaluated. They were assessed by means of clinical history and examination, blood urea, creatinine and electrolyte estimation, urinary flowmetry and ultrasound scan of the whole urinary tract.

Abnormal urea estimations were noted if > 6.5 mmol/l and abnormal creatinine if > 120 μ mol/l. Flow rates suggestive of obstruction were those less than 15 ml/s if the volume voided exceeded 100 ml. A residual volume > 100 ml was deemed abnormal. Associated abnormalities of the upper tract were noted and the final outcome recorded.

Clinical evaluation of a palpable bladder was

found to be an unreliable method of estimating the volume of residual urine and hence was not studied.

Results

The mean age of the 223 patients was 69.60 ± 8.35 years (1 SD) (range 51–87 years). Upper tract abnormalities detected on ultrasound scan are listed in Table 1. Ultrasound scans (USS) of the lower tract showed 80 patients to have residual urine volumes exceeding 100 ml. Five patients had diverticula, 1 a bladder calculus and 1 a bladder tumour.

A total of 67 patients were discharged from the clinic following investigation and 39 remain on the waiting list (> 1 year); 95 patients have undergone prostatic surgery, 90 by transurethral resection of the prostate (69 benign and 21 malignant), 4 by bladder neck incision and 1 by retropubic prostatectomy. Thirteen patients were diagnosed as having detrusor instability.

The ability of the different tests to detect the presence of hydronephrosis is presented in Table 2. The features of patients with hydronephrosis are presented in Table 3, as are the abnormalities revealed on ultrasound scanning.

Discussion

In the assessment of bladder outlet obstruction, ultrasound has often been contrasted with intravenous urography (Matthews *et al.*, 1982; Lilianfield *et al.*, 1985; Fidas *et al.*, 1987; Stavropoulos *et al.*, 1988). Ultrasonography of the bladder is cheap, safe and reliable and can be carried out in the urological department, but few studies have been made of its value in assessing the upper urinary tract. Bauer *et al.* (1980) suggested that blood urea estimation was useful in predicting upper tract dilatation but this was not found to be the case in

Table 1 Abnormalities Detected on Ultrasound Scanning of the Upper Urinary Tract

Abnormality	No. of patients
Hydronephrosis	17 (7.6)
Renal cysts	40 (17.9)
Renal carcinoma	1 (0.4)
Renal calculus	1 (0.4)
Gall bladder calculus	5 (2.0)
Aortic aneurysm	1 (0.4)

Figures in parentheses indicate % abnormalities expressed per total number of scans.

Table 2 Patients with Hydronephrosis and Other Abnormalities. Sensitivity, Specificity and Positive Predictive Value

	Hydro-nephrosis	No hydro-nephrosis	Value of test %
Urea (mmol/l) > 6.5	8	58	Sensitivity 47
Urea < 6.5	9	148	Specificity 72 PPV* 12
Urea > 8.5	7	21	Sensitivity 41
Urea < 8.5	10	185	Specificity 89 PPV 25
Creatinine (μ mol/l) > 120	10	58	Sensitivity 58
Creatinine < 120	7	148	Specificity 72 PPV 25
Creatinine > 150	7	5	Sensitivity 41
Creatinine < 150	10	201	Specificity 97 PPV 28
Residual urine (ml) > 100	8	72	Sensitivity 47
Residual urine < 100	9	134	Specificity 65 PPV 10
Residual urine > 150	7	56	Sensitivity 41
Residual urine < 150	10	150	Specificity 73 PPV 11
Flow rate (ml/s) < 15	13	91	Sensitivity 93
Flow rate > 15	1	44	Specificity 33 PPV 13

*PPV = Positive predictive value.

Table 3 Features of Patients with Hydronephrosis

Urea > 6.5 mmol/l	Creatinine > 120 μ mol/l	Residual urine > 100 ml	Flow rate > 15 ml/s	Volume voided (ml)
<i>Moderate or severe hydronephrosis</i>				
6.4	167	900	4	60
17.6	452	535	NR*	NR
5.2	93	450	17	414
4.6	82	163	NR	NR
47.3	1540	15	4	69
9.1	180	565	4	135
<i>Mild hydronephrosis</i>				
7.7	125	480	3	90
5.6	102	26	14	303
5.9	109	46	9	66
12.0	189	77	8	118
4.8	98	500	4	145
4.0	127	82	14	346
10.2	171	94	6	91
9.7	128	27	11	81
4.9	116	148	11	231
10.9	151	0	NR	NR
4.7	112	97	9	401

*NR = Not recorded.

the study by De Lacey *et al.* (1988). None of the patients in De Lacey's series with hydronephrosis had raised blood urea. In our study of the 17 patients with hydronephrosis, 8 had raised plasma urea and this was evenly distributed between mild hydronephrotics (5/11) and 3 of 6 in the moderate to severe group (Table 3); creatinine also failed to discriminate. Four of 6 patients had a raised creatinine in the moderate to severe hydronephrotics and 6 of 11 in the mild group. This would still allow 7 patients to slip through the net if it were used as a screening test for USS and would also result in 58 unnecessary scans in patients whose creatinine exceeded 120 $\mu\text{mol/l}$ with no evidence of dilated upper tracts (Table 2). Improved specificity would occur if the point at which results were deemed abnormal were altered (e.g. urea > 8.5 mmol/l, creatinine > 150 $\mu\text{mol/l}$) but there would be a loss of sensitivity (Table 2).

If blood tests are not useful, would a significant volume of residual urine (> 100 ml) help to determine patients likely to have upper tract dilatation? Of the 17 patients with hydronephrosis, 9 had residual urines < 100 ml and 8 > 100 ml. In addition, the use of USS for estimating residual urine has been questioned (Birch *et al.*, 1988). Others decide on operative intervention according to residual volume and flowmetry results (Abrams, 1977; Stott *et al.*, 1988). Abnormalities in the flow rate appear to be sensitive but are not very specific in detecting hydronephrosis (Table 2); in the present series, 40 patients failed to provide an evaluable flow rate.

It appears that neither estimation of plasma urea and creatinine, nor residual urine nor flowmetry will predict the presence of hydronephrosis. To adopt the plain X-ray film measurement for residual urine (Timoney *et al.*, 1989) also fails to assist decision-making regarding urgency for operation.

Cascione *et al.* (1987) stated that the use of USS had little impact on a patient's management in the absence of normal blood and urine investigations. With this we would disagree.

With regard to other abnormalities we agree with Talner (1986) and O'Reilly (1987) that there is a low pick-up rate for renal carcinoma or incidental aortic aneurysms (0.4% of patients each) (Table 1). We feel this cannot be used as an argument for scanning the upper tracts. Nevertheless, we believe that USS of the upper tracts should be retained to ensure that patients with evidence of upper tract dilatation receive priority.

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The Sonographic Appearance of Irradiated Prostate Cancer

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Summary—Transrectal ultrasonography of the prostate was performed before radical prostatectomy in 22 patients with persistent or recurrent cancer after definitive radiotherapy. Serial transverse sonograms were compared with whole-mount step-sections of the prostatectomy specimens to evaluate the sonographic features of irradiated prostate cancer. To define more clearly the effects of radiation on malignant prostatic tissue, we assessed the degree of histological change induced by the irradiation (radiation effects) as none, mild, moderate or severe. A total of 121 areas of cancer > 4 mm in maximum diameter were identified on the histological sections. Of these, 105 (87%) showed no radiation effects or mild effects, and 72% (76/105) of these appeared hypoechoic on the corresponding sonogram. There were 16 foci with moderate or severe radiation effects and only 25% (4/16) appeared hypoechoic. The remaining 12 foci were isoechoic.

Areas of cancer which show moderate or severe radiation effects tend to become isoechoic while large (> 4 mm) foci of cancer in the irradiated prostate usually show little radiation effect, and these foci typically appear hypoechoic.

Although marked histological changes are known to occur in the prostate as a result of radiotherapy (Bostwick *et al.*, 1982; Fajardo, 1982), few reports have described the effects of radiotherapy on the sonographic features of the prostate and of prostate cancer (Pontes *et al.*, 1984; Lee *et al.*, 1988; Egawa *et al.*, 1989a, b; Kabalin *et al.*, 1989). Lee *et al.* (1988), on the basis of biopsy results, noted that the criteria used to detect cancer in the irradiated prostate were similar to those used in the non-irradiated prostate. In our experience with sonography of the irradiated prostate, large hypoechoic lesions (> 5 mm in minimum diameter) usually corresponded to areas of cancer in radical prostatectomy specimens taken from patients who had failed to respond to radiotherapy (Egawa *et al.*, 1989a) (Fig. 1).

A unique opportunity to compare whole-mount sections of prostates removed from 22 patients whose cancer had recurred after radiotherapy with the corresponding sonograms of the prostate ob-

tained pre-operatively allowed us to examine the sonographic features of known cancer after irradiation and to evaluate the histological changes induced by radiation.

Patients and Methods

Between January 1984 and August 1988, radical prostatectomy was performed in 25 patients with clinical local recurrence of prostate cancer after definitive radiotherapy (Neerhut *et al.*, 1988; Goldstone *et al.*, 1990). Pre-operative sonographic studies were performed in 22 of these patients, aged 55 to 72 years (mean 64). None received hormonal therapy. The clinical stage at the time of radical prostatectomy in 2 patients was A2 (> 3 microscopic foci or less than well differentiated); in 11 it was B1 (palpable induration, 1 lobe); in 7 it was B2 (both lobes) and in 2 it was C1 (extension into seminal vesicles but < 6 cm). The results of histological grading of the initial cancer were available from the hospital records for 19 patients: 5 tumours were well differentiated, 9 were moderately differ-

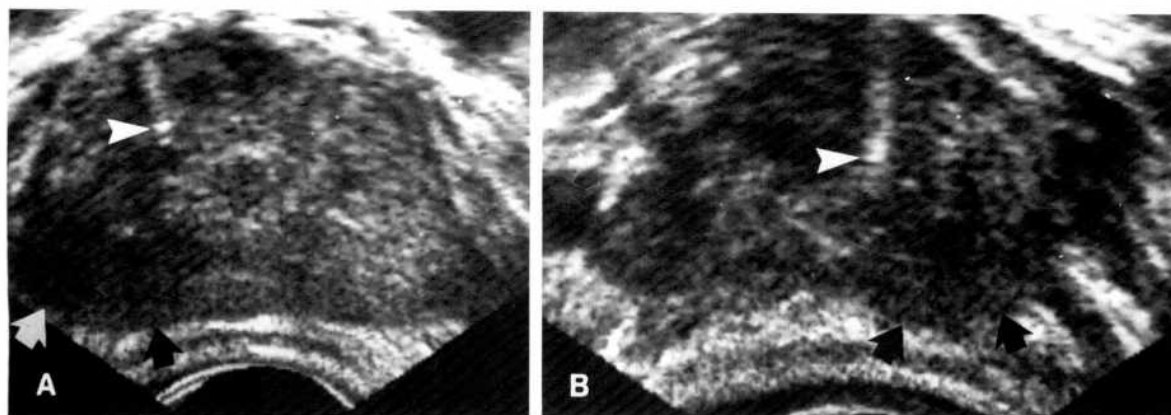


Fig. 1 Representative case of recurrent prostate cancer 20 months after radiotherapy (gold seed implantation with external beam irradiation). (A) Ultrasound scan, transverse image. (B) Ultrasound scan, longitudinal image. A very discrete hypoechoic lesion is seen in the right peripheral zone (arrows). Ultrasound-guided biopsy of the lesion revealed recurrent prostate cancer, Gleason sum 7. The non-malignant prostate gland retains its finely stippled internal echo pattern. A gold seed is visible (arrowhead).

entiated and 5 were poorly differentiated. Fifteen patients were treated with implantation of radioactive gold seeds followed by external beam irradiation, 6 with external beam irradiation only, and 1 with implantation of ^{125}I only. The mean dosage of irradiation therapy (excluding the patient with ^{125}I implantation) was 7500 cGy (range 6420–9000). The mean interval from radiotherapy to radical prostatectomy was 45.9 months (range 15–126).

The Aloka SSD-502 or 520 chair-type transrectal ultrasonic radial scanners were used. These machines were equipped with chair-mounted 5.0 MHz radial probes (12 patients) or 7.0 MHz radial probes (10 patients) and produced serial transverse sections of the prostate and the seminal vesicles. Continuous scanning was performed from the apex of the prostate to the tip of the seminal vesicles and representative images were recorded on polaroid film at 2 to 5 mm intervals.

Prostates were sectioned serially in the transverse plane from apex to base at 5 mm intervals. Tumour maps traced directly from whole-mount step-sections were compared with pre-operative transrectal ultrasonograms. Discrete and separate areas of cancer >4 mm in maximum diameter in the transverse plane on the tumour maps were identified and compared with the corresponding sonogram. In our experience, foci <4 mm are outside of the range of visibility on ultrasound (Shinohara *et al.*, 1989a, b). Once an area of cancer >4 mm in maximum diameter had been identified and classified, its sonographic appearance could be evaluated in relation to the size of the lesion (maximum

diameter), tumour differentiation (Gleason sum) and radiation effect.

Histological changes related to radiotherapy were evaluated in each area of cancer. These changes were graded microscopically on a semiquantitative scale ranging from none to severe by one of the authors (T.M.W.). If the degree of radiation effect varied within a single focus of cancer, as sometimes happened, the predominant pattern was used. Radiation effects on residual cancer are shown in Figure 2. The following system was used for classification: **none**, tumour indistinguishable from non-irradiated tumour; **mild**, minimal cytological and/or architectural derangements in the tumour; **moderate**, moderate cytological and/or architectural derangements in the tumour, although tumour cells still appear viable; **severe**, advanced cytological and/or architectural derangements in the tumour cells which appear non-viable morphologically. The tumours could be broadly classified into 2 groups for further evaluation: those showing "minimal" effects (none to mild) and those showing "marked" effects (moderate to severe).

Results

In all, 124 sections were obtained from the 22 radical prostatectomy specimens and 121 areas of cancer >4 mm in maximum diameter in the transverse plane were identified on the tumour maps. Of the 121 areas, 105 (87%) showed minimal radiation effects and 16 (13%) showed marked effects. Each area of cancer on a given section could easily be classified as having either minimal or

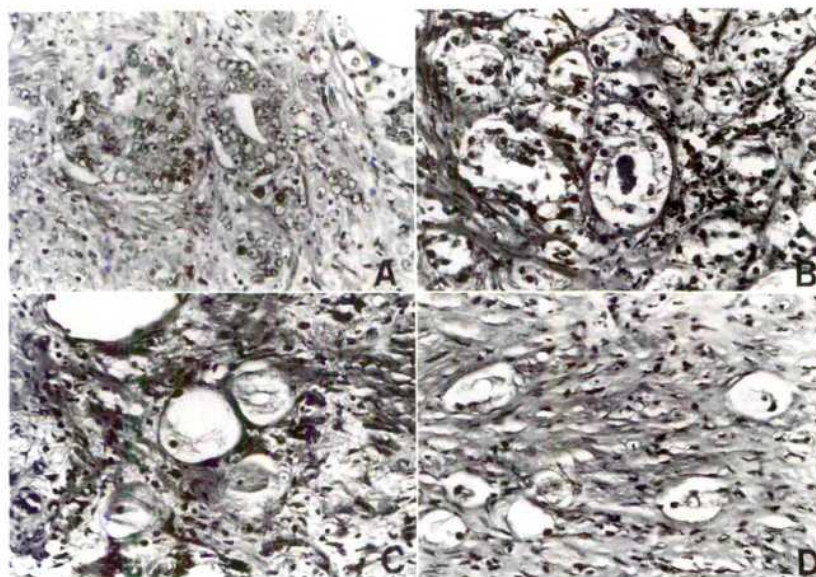


Fig. 2 Pathological classification of radiation effects on residual prostate cancer following definitive radiotherapy. (A) No radiation effect. (B) Minimal radiation effect. (C) Moderate radiation effect. (D) Severe radiation effect. (H and E $\times 325$).

marked radiation effects respectively. In general, the radiation effects on the cancer were uniform throughout any given prostate, although in 4 cases a mixture of minimal and marked radiation effects was seen (Fig. 3). These 4 patients had been treated with gold seed implantation followed by external beam irradiation.

No correlation was found between pre-radiotherapy tumour differentiation, post-operative tumour differentiation and radiation effects.

Of the 121 separate areas of cancer >4 mm in maximum diameter, 80 (66%) were hypoechoic, 36 (30%) were isoechoic and 5 (4%) were hyperechoic. Among the 105 areas of cancer with minimal

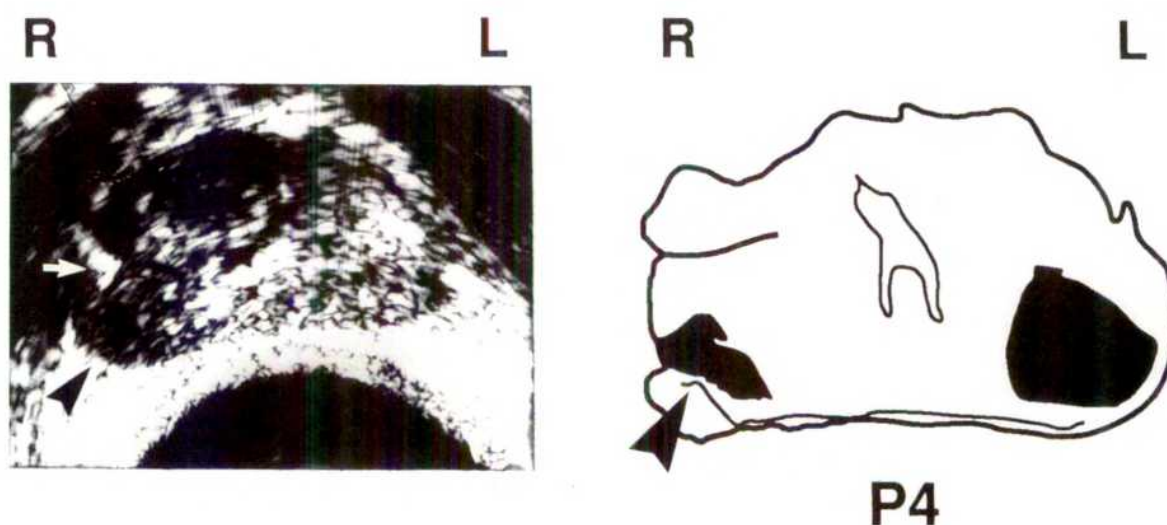


Fig. 3 Representative case showing the difference in echogenicity related to the radiation effect. The tumour map at the same level as the transrectal sonogram illustrates 2 separate foci of residual prostate cancer. While the right lesion with minimal radiation effect appears hypoechoic (arrowhead), the larger left lesion with marked radiation effect appears isoechoic. A gold seed is seen (arrow).

radiation effect, 76 (72%) were hypoechoic. Among the 16 areas of cancer with marked radiation effect only 4 (25%) were hypoechoic (Table 1). The larger the tumour, the more likely it was to be hypoechoic (Table 2). There was also a relationship between size and radiation effect (Fig. 4). In the group with marked radiation effect, 75% of the tumours were <10 mm in diameter. In the group with minimal effect, only 27% were <10 mm. There was no correlation between grade and echogenicity in this small group of patients, but none of the tumours was well differentiated. Overall, 72% of the tumours with Gleason sums 5 to 7 (moderately differentiated) were visualised, and 67% of the tumours with Gleason sums 8 to 10 (poorly differentiated) (48% were hypoechoic and 19% were hyperechoic).

Table 1 Relationship between Tumour Echogenicity and Radiation Effect for Tumour Foci > 4 mm

	Radiation effect	
	Minimal No. (%)	Marked No. (%)
Hypoechoic	76 (72)	4 (25)
Isoechoic	24 (23)	12 (75)
Hyperechoic	5 (5)	—
Total	105	16

Table 2 Relationship between Tumour Echogenicity and Size

	Tumour size (maximum diameter)		
	< 5 mm No. (%)	5–10 mm No. (%)	> 10 mm No. (%)
Hypoechoic	—	14 (41)	66 (81)
Isoechoic	6 (100)	18 (53)	12 (15)
Hyperechoic	—	2 (6)	3 (4)
Total	6	34	81

Discussion

Although prostate cancer typically appears hypoechoic on transrectal ultrasonography (Lee *et al.*, 1985; Dähnert *et al.*, 1986; Salo *et al.*, 1987; Shinohara *et al.*, 1989a, b), the appearance of cancer in the irradiated prostate has not been clear (Pontes *et al.*, 1984; Lee *et al.*, 1988; Egawa *et al.*, 1989a, b; Kabalin *et al.*, 1989). The histological changes induced by radiotherapy in the non-malignant prostate (Bostwick *et al.*, 1982; Fajardo

et al., 1982)—decreased number of glands—have been assumed to cause a relatively hypoechoic appearance. Kabalin *et al.* (1989) recently reviewed 27 ultrasound-guided needle biopsies of the prostate at least 18 months after radiotherapy and found hypoechoic lesions in 26 of 27 patients. Ultrasound-guided biopsies of hypoechoic areas were positive for cancer in 69% of cases (18/26) and the positive predictive value of a focal hypoechoic lesion was 75% (12/16). The “false positive” hypoechoic areas were reported to be severe radiation-induced atrophy. They concluded that ultrasound findings correlated poorly with pathological findings in the irradiated prostate. However, 93% of their patients were found to have persistent cancer by either directed or systematic biopsy. Such a high frequency of positive biopsy results after radiotherapy implies that radiotherapy is incapable of eradicating prostate cancer, yet long-term results of treatment trials have shown that many patients survive for many years without clinical evidence of recurrent cancer (Bagshaw *et al.*, 1988; Scardino and Wheeler, 1988), casting doubt on the clinical significance of finding small foci of cancer on random biopsies.

Lee *et al.* (1988) noted that anechoic or hypoechoic lesions following radiotherapy frequently represented persistent cancer and the positive predictive value of such lesions for cancer was 91%. Our experience is similar and supports the view that non-malignant prostate tissue generally retains its normal echogenic appearance after irradiation (Egawa *et al.*, 1989a, b).

The histological changes in prostate cancer induced by radiotherapy have been described as quantitative: a decrease in the number of malignant glands (Bostwick *et al.*, 1982; Fajardo *et al.*, 1982). We found, however, that there were also quantitative changes in the appearance of the malignant glands, primarily cytological rather than architectural, and we have developed a semi-quantitative classification of radiation effects based upon microscopic criteria in order to study how such radiation effects could alter the sonographic appearance of prostate cancer. Dhom and Degro (1982) similarly used a 10-point score of regression to classify biopsy results after radiotherapy. We classified radiation effects into 4 categories (none, mild, moderate and severe) according to the degree of architectural and cytological derangement. Our results show that these radiation effects may alter the sonographic appearance of cancer after radiotherapy.

The sonographic appearance of prostate cancer is relative and results from the contrast between tumour and the normal tissue of the prostate

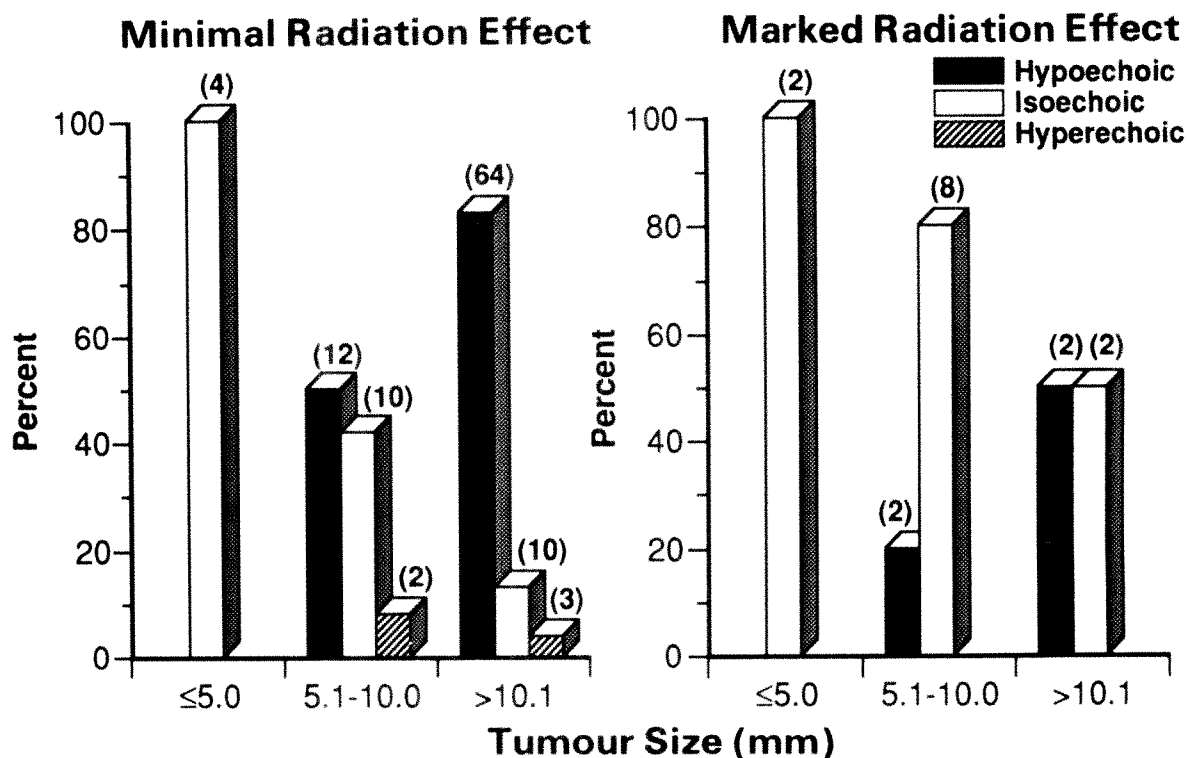


Fig. 4 Correlations between echogenicity and tumour size grouped by degree of radiation effect. Figures in parenthesis represent numbers of tumour areas of each size.

(Scardino, 1989; Shinohara *et al.*, 1989a, b). In the irradiated prostate, histological changes induced by irradiation would be expected to alter the echo characteristics of the normal tissue as well as the cancer. Factors not present in the untreated prostate may therefore affect the echo pattern of cancer in the irradiated prostate. Among these factors may be radiation-induced atrophy of glands in both normal and malignant tissue. Thus, when radiation effects were minimal, 72% of the cancers appeared hypoechoic. When radiation effects were marked, however, only 25% of the cancers were hypoechoic. The isoechoic appearance of cancers with marked radiation effect may be related to the loss of malignant glands or to a blending of the irradiated cancer with the surrounding non-malignant tissue (Fig. 2). Miller (1989) suggested that the intensity and pattern of the reflected echoes from an area of the prostate may be related to the relative proportion of epithelial and stromal elements present. This factor may play a role in irradiated prostate cancer as well. Another important cause of the isoechoic appearance of cancers with a marked radiation effect is the smaller size of most of these

tumours. Most of the larger tumours in this study tended to appear hypoechoic, as has been observed in non-irradiated prostates (Scardino, 1989; Shinohara *et al.*, 1989a, b).

Our results suggest that prostate cancer which persists after radiotherapy usually appears hypoechoic, as does untreated prostate cancer. Results in our ongoing studies with newer equipment (Bruel & Kjaer 1846 scanner) and a 7 MHz biplanar transducer are consistent with these findings. Tumours with minimal radiation effects usually appear hypoechoic, while most foci of cancer with marked radiation effects tend to be isoechoic because of the diminished size of the tumour and the scarce distribution of glands with atrophic and flattened glandular epithelium often intermixed with similar appearing non-malignant prostate tissue.

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Early Endoscopic Realignment of Complete Traumatic Rupture of the Posterior Urethra

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Summary—Early primary endoscopic realignment of complete traumatic rupture of the posterior urethra is a simple, rapid and non-traumatic technique. We have recently treated 5 patients in this manner. All are continent and 4 are potent. Four patients were followed up for 1 year. One patient required no further management and had excellent urinary flow rates. The other 3 developed short secondary strictures which were managed successfully by 1 or 2 internal urethrotomies.

Webster *et al.* (1983) reported that 10% of pelvic fractures are associated with posterior urethral disruption; 75% of these injuries are due to road accidents (Palmer *et al.*, 1983; Bouchot *et al.*, 1989) and are frequently associated with vascular, abdominal, orthopaedic or neurological injuries.

The classical surgical management of a disrupted urethra is primary suprapubic cystotomy and delayed urethroplasty. This yields good results for urethral continuity but there is a 14 to 25% rate of secondary stricture (Morehouse, 1988; Bouchot *et al.*, 1989). The major risk with this approach is enhancing post-traumatic impotence, which can occur in up to 40% of patients (Gibson, 1970).

Early endoscopic realignment of complete posterior urethral rupture is a safe, rapid and non-traumatic technique. It corrects lateral urethral displacement at the rupture site and permits anatomical healing in 40% of cases. It also obviates the risk of increasing post-traumatic impotence due to pudendal nerve injuries.

We have managed 5 patients with this technique and present the results.

Patients and Methods

Between October 1987 and April 1990, 5 patients with complete posterior urethral disruption and

traumatic fractures of the bony pelvis were managed by early endoscopic realignment. The age range was 19 to 57 years (mean 43). The injuries were due to road accidents in 4 cases and an accident at work in 1 case.

Urethral bleeding, urinary retention and perineal haematoma were present in all 5 patients.

In all cases immediate intravenous urography was carried out and demonstrated upper urinary tract integrity, bladder elevation without bladder injury and absence of antegrade urethral opacification. Suprapubic bladder catheterisation was undertaken as soon as possible. In 1 patient with an associated hypogastric artery injury, angiographic embolisation was necessary.

Early urethral endoscopic realignment was performed as soon as vascular and orthopaedic injuries were controlled and local haemostasis had been obtained from tamponade (2–10 days).

Technique

The procedure is carried out by 2 operators. The patient is placed in the lithotomy position. The first operator (A) explores the anterior urethra up to the rupture site by retrograde urethroscopy. The haematoma is washed out as much as possible. The second operator (B) dilates the suprapubic catheter tract, places a 20 F Amplatz sheath into the bladder and uses a cystoscope to explore the bladder, the bladder neck and the posterior urethra down to the

rupture site. In one case the 2 cystoscopes "met", allowing operator A to pass the urethroscope into the bladder. In the other cases, operator B inserted a 7 F ureteric stent into the posterior urethra and then pushed it down to the rupture site. It was easily seen by operator A, who was able to grasp it with biopsy forceps and pull it out through the external meatus.

The ureteric stent then acts as a guide for a perforated 18 F silicone Foley catheter which is passed into the bladder. Operator B is able to control, under direct vision, the correct positioning of the catheter and filling of its balloon on the bladder neck.

The Foley catheter is left in place for 3 weeks and suprapubic drainage continues for 1 month.

Suprapubic cystography and urethrography are performed after 3 weeks' stenting. The Foley catheter is removed if there is no extravasation of contrast medium, urethral displacement or stricture and no post-voiding residue. If contrast medium extravasation is present, the suprapubic catheter is left in place for a further 2 weeks.

Results (Table)

Patients were hospitalised for periods of 21 to 45 days (mean 29), mainly for orthopaedic reasons. During this period no perineal infection was observed.

Immediate results

One patient showed extravasation of contrast medium at the disruption site when the urethral catheter was removed (antegrade urethrogram). In this case the suprapubic drainage was continued for an extra 15 days.

All patients voided satisfactorily and were completely continent when the urethral stent was removed. No patient had any post-voiding residue.

Four of the 5 patients were potent.

Medium-term results (2 months)

Two patients required no further treatment; 1 had excellent urinary flow rates (25 ml/s) and no residual urine while the other had moderately good flow rates (13 ml/s) with 150 ml of residual urine.

The remaining 3 patients had short urethral strictures with decreased flow rates (< 5 ml/s). They were managed by direct vision internal urethrotomy 6 to 8 weeks after realignment. One patient had an excellent result which was maintained at 1 year. The other 2 developed recurrent strictures and were managed successfully by repeat urethrotomy. Follow-up flow rates at 6 months were 20 ml/s and there was no residual urine after voiding.

All patients were continent; 1 remained impotent.

Long-term results (1 year)

Four patients have been evaluated and all have a good flow rate (> 20 ml/s) with no residual urine; all have remained continent. Three patients have normal erections and the fourth has remained impotent throughout the study.

Discussion

The management of patients with traumatic posterior urethral disruption remains controversial and many techniques have been proposed.

Immediate end-to-end anastomosis or surgical exploration with realignment over a catheter exposes the severely injured patient to further risks. The operation can be complicated by considerable haemorrhage and/or by difficulty in assessing precisely the viability of the 2 ruptured urethral extremities. Secondary stricture, incontinence and impotence rates are also high (Le Guillou and Ferrière, 1983; Webster *et al.*, 1983; Morehouse, 1988).

Immediate cystotomy and delayed surgical repair are currently regarded as the treatment of choice.

Table Short- and Long-term Results

Patient no.	Age (years)	1 month				Complementary management	1 year		
		Flowmetry (ml/s)	Continence	Potency			Flowmetry (ml/s)	Continence	Potency
1	34	5	+	+	2 urethrotomies	20	+	+	
2	19	20	+	+	—	22	+	+	
3	57	25	+	+	1 urethrotomy	22	+	+	
4	57	5	+	—	2 urethrotomies	20	+	—	
5	46	13	+	+	—				

Surgical repair can be performed 10 days after the trauma, when haemostasis has occurred and before fibrosis has developed. The repair usually consists of an end-to-end anastomosis of the urethral ends. The secondary stricture rate is 25%, with a 38% impotence rate. Secondary incontinence is unusual (Ridoux and Lobel, 1983; Webster *et al.*, 1983; Bouchot *et al.*, 1989).

Surgical repair can be performed after a delay of 3 months using a 2-stage (Johansen, 1953) or a 1-stage urethroplasty (Webster *et al.*, 1983; Morehouse, 1988). As far as urethral permeability and continence are concerned, the results are very good (Webster *et al.*, 1983; Morehouse, 1988). However, the main drawback of these techniques is the long period during which the patient has a cystotomy before being readmitted to hospital for definitive surgery.

Many primary realignment techniques, using various interlocking sounds with or without traction, have been proposed. Their secondary stricture rate, impotence and incontinence rates are 69, 44 and 20% respectively (Webster *et al.*, 1983; Morehouse, 1988). The main criticism of these techniques, in addition to their poor results, is that they are performed blindly and there is a risk of creating a false passage.

Primary endoscopic realignment is an interesting option. The procedure is performed as soon as haemodynamic conditions are controlled, orthopaedic injuries stabilised and local haemostasis has been obtained by tamponade. This rapid and non-aggressive technique provided definitive treatment for 1 of our patients and led to continence in all 5 cases and normal erections in 4. The secondary stricture rate was high (60%) but these strictures were short (<2 cm) and were managed successfully by 1 or 2 internal urethrotomies. We think it likely that these strictures were caused by a degree of ischaemia of the 2 urethral extremities rather than displacement, which is corrected by the realignment at least in its lateral component.

The risk of introducing infection to the perineal haematoma exists but seems minor (Gelbard *et al.*, 1989). No perineal infection was observed in our series.

Primary endoscopic realignment of traumatic posterior urethral disruption is a simple, non-traumatic, safe and rapid technique. It not only enables the surgeon to identify incomplete urethral disruption, which can be stented easily (3 other

patients were in this category during the same period), but also permitted complete endoscopic management of all of our patients. In case of an eventual failure of repeat urethrotomy, we believe that endoscopic realignment will probably facilitate secondary surgical management by reducing the lateral urethral displacement and washing out part of the perineal haematoma, which is an important source of fibrosis.

Our results confirm those of Gelbard *et al.* (1989), who have managed 7 patients with a similar technique, and encourage us to continue to use this technique as the primary management of complete posterior urethral ruptures.

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Colour Duplex Sonography in the Assessment of Impotence

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Summary—We present our experience with colour duplex sonography (Acuson 128) in the assessment of 83 impotent men. Cavemosal artery measurements were taken before and after the intracorporeal injection of papaverine. The peak velocities following papaverine injection correlated well with the degree of clinical response. Percentage diameter change corresponded with some groups of clinical erection grade, although it was not as good a discriminator as peak velocity.

Twelve patients with 24 cavemosal arteries were also examined using pharmacological selective arteriography. Correlation between duplex sonography and arteriography showed an accuracy of 87.5%, specificity of 100.0% and sensitivity of 82.4%.

All patients with a clinically good response following papaverine injection had peak bilateral cavemosal artery velocities ≥ 25 cm/s. Amongst the remaining suboptimal responders, 18 also had this finding. Fifteen of these underwent pharmacological cavemosalography and 14 exhibited venous leakage.

Duplex sonography is a valuable and non-invasive tool in the assessment of impotence and can provide valuable information in deciding the course of further evaluation and treatment. The procedure was always completed more quickly with the guidance of colour Doppler.

Vasculogenic impotence was first evaluated by means of high-resolution sonography and quantitative Doppler spectrum analysis by Lue *et al.* (1985). However, it is time-consuming both to identify and establish the effect of papaverine on both cavemosal arteries with conventional duplex sonography.

The use of colour duplex sonography could obviate these shortcomings. The entire procedure, comprising identification, diameter measurement and calculation of flow velocity of the cavemosal arteries, is completed within 1 min. Thereafter, the cavemosal artery peak velocity can be recorded correctly.

We present our experience in the assessment of the response to intracorporeal papaverine injection using this method and compare the results with the clinical assessment, selective arteriography and other penile haemodynamic measurements.

Patients and Methods

Eighty-three impotent men (aged 20–87 years) were included in this study. They also represented various other clinical aetiologies (Table 1). Prior to colour duplex sonography, each patient underwent a thorough history, physical examination and endocrine survey (FSH, LH, prolactin, testosterone).

Table 1 Patients with Other Clinical Aetiologies

Aetiology	No.
Diabetes	11
Hypertension	7
Myocardial infarction	3
Arrhythmia	6
Retrograde ejaculation post-TURP	3
Spondylolisthesis	2
Penile injury	1
Psychogenic	2
Peyronie's disease	4
Total	39

We used a computed sonography system (Acuson 128) with an imaging frequency of 10 MHz and pulsed Doppler with a frequency of 5 MHz. The colour Doppler imaging option can provide an imaging technique that allows real-time spatial visualisation of blood flow velocity patterns in vascular structures. Blood flow towards the transducer appears in red and flow away from the transducer appears in blue. Thus the cavernosal artery can easily be visualised as red in the corpus cavernosum.

The papaverine test identified 4 grades of erection (Table 2) and was always evaluated by a single examiner.

Table 2 Papaverine Test

Erection grade	No. of patients
0-No response	1
1-Tumescence but no rigidity	25
2-Sub-optimal erection	41*
3-Normal erection	16†

* Includes 18 with bilateral cavernosal artery peak velocity ≥ 25 cm/s.

† All with bilateral cavernosal artery peak velocity ≥ 25 cm/s

All patients underwent measurement of the diameter and velocity of the cavernosal arteries bilaterally in the flaccid state. Thereafter, a rubber band was placed at the base of the penis and 30 mg of papaverine were injected into either corpus cavernosum with a 26-gauge needle. The dosage was adjusted to 60 mg for large penises in a few patients. The rubber band was cut after 2 min and the diameter and velocity were then assessed immediately. The duration of each assessment averaged 1 to 2 min. The procedure was repeated until the peak velocity had been measured. The duplex scanning was always performed by a single experienced examiner to save time, to ensure accurate measurement of peak velocity and to avoid artificial errors in the measurement of diameter. The total duration of the examinations averaged 20 to 30 min for each patient.

In 12 of the 83 patients examined by colour duplex sonography, additional selective arteriography was also performed. Initially, the aortic bifurcation and common iliac vessels were inspected. The second angiogram was obtained 5 min after the intravenous injection of morphine and

intracorporeal injection of papaverine. The third angiogram was obtained 10 to 15 min after this injection. Injection of papaverine through an angiocatheter was also performed in 4 patients.

Fifteen of 18 patients with peak velocities ≥ 25 cm/s and sub-optimal erection underwent pharmacological cavernosography. A rubber band was tightly placed at the base of the penis and 60 mg papaverine were injected through a 24-gauge butterfly needle inserted into the corpora cavernosa. The rubber band was removed 2 min later. In patients in whom papaverine did not produce an erection adequate for erection cavernosography, additional saline was given at the rate of 80 ml/min until either an adequate erection was reached or a total of 100 ml had been delivered. Contrast material (20 ml) was then injected for X-ray visualisation of abnormal veins.

Results

The peak velocity, and velocity changes after papaverine injection, corresponded well ($P < 0.01$) with clinical erection grade (Table 3). All patients within erection grade 3 exhibited bilateral cavernosal artery peak velocities ≥ 25 cm/s. Of the 41 sub-optimal responders, 18 produced the same results.

Table 3 Cavernosal Artery Peak Velocity Changes before and after Intracorporeal Papaverine Injection

Erection grade	Peak velocity (cm/s)		
	(Before PAP)	(After PAP)	Increase
0 (n=1)	0	5.5	5.5
1 (n=25)	6.75 $\pm$ 5.61	16.82 $\pm$ 5.18	10.08 $\pm$ 5.00
2 (n=41)	8.12 $\pm$ 6.21	27.60 $\pm$ 6.54	19.48 $\pm$ 8.20
3 (n=16)	7.66 $\pm$ 3.92	43.48 $\pm$ 13.13	35.82 $\pm$ 13.10
<i>Statistical analysis</i>			
1 v 2	ns	$P = 0.0001^\dagger$	$P = 0.0001^*$
2 v 3	ns	$P = 0.0002^\dagger$	$P = 0.0001^*$
3 v 1	ns	$P = 0.0001^\dagger$	$P = 0.0001^*$

* Wilcoxon rank sum test for non-parametric data

† Unpaired *t* test for parametric data

ns: not significant at 5% level

The percentage of diameter increase also corresponded (1 v 2, $P < 0.05$; 3 v 1, $P < 0.05$) with clinical erection grade (Table 4).

Table 4 Cavernosal Artery Diameter Changes before and after Intracavernosal PAP Injection

Erection grade	Diameter (mm)		Diameter increase (%)
	(Before PAP)	(After PAP)	
0 (n=1)	0.45	0.55	22.22
1 (n=25)	0.43 ± 0.09	0.57 ± 0.12	37.04 ± 36.93
2 (n=41)	0.38 ± 0.10	0.60 ± 0.16	63.68 ± 47.63
3 (n=16)	0.38 ± 0.12	0.67 ± 0.17	75.28 ± 55.34
<i>Statistical analysis:</i>			
1 v 2	P=0.0354†	ns†	P=0.0177*
2 v 3	ns†	ns†	ns*
3 v 1	ns†	P=0.0474†	P=0.0270*

* Wilcoxon rank sum test for non-parametric data

† Unpaired *t* test for parametric data

ns: not significant at 5% level

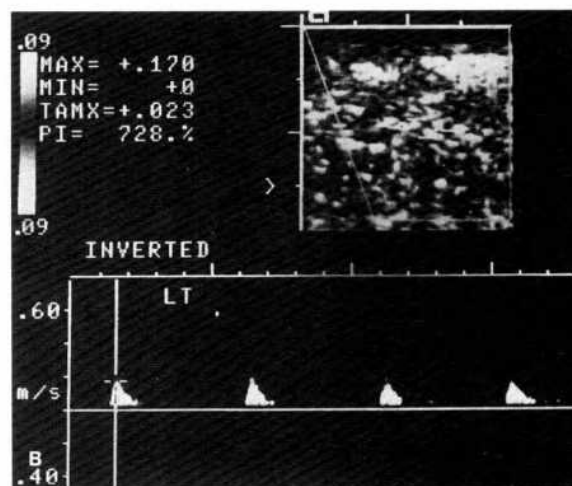
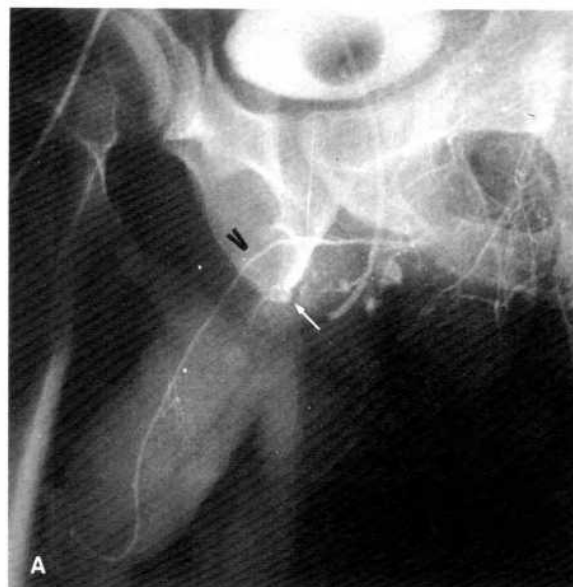
Doppler and arteriographic findings were compared in 12 patients (24 cavernosal arteries) (Table 5). In 14 cavernosal arteries with hypoplasia, aplasia, arteriosclerotic stenoses or occlusion were seen by both angiography and duplex sonography (peak velocity < 25 cm/s); these were true positives (Fig. 1). In 3 cavernosal arteries, peak velocities were ≥ 25 cm/s despite there being no visualisation of the cavernosal artery in arteriograms; these were false negatives. Seven normal arteriograms with peak velocities ≥ 25 cm/s were noted; these were true negatives (Fig. 2). A normal arteriogram with abnormal peak velocity (< 25 cm/s) was not found, *i.e.* a false positive.

Table 5 Correlation of Colour Duplex Sonography and Selective Angiography

	Angio pathological	Angio normal
Peak velocity < 25 cm/s	14 (tp)	0 (fp)
Peak velocity ≥ 25 cm/s	3 (fn)	7 (tn)

tp: true positive; tn: true negative; fp: false positive; fn: false negative.

The sensitivity of colour duplex sonography in detecting pathological changes in the cavernosal arteries was found to be 82.4%; specificity was 100.0%; overall accuracy was 87.5% (Table 6).

**Fig. 1** A 41-year-old patient with erectile dysfunction of 3 years' duration. (A) The arteriogram shows occlusion of cavernosal artery with helicine arteries (arrow) and good visualisation of the dorsal artery (arrow head). (B) The peak velocity after papaverine injection is 17 cm/s.

Of the 41 sub-optimal responders, 18 exhibited bilateral cavernosal artery peak velocities ≥ 25 cm/s. Fifteen of 18 underwent pharmacological cavernosography and 14 exhibited venous leakage.

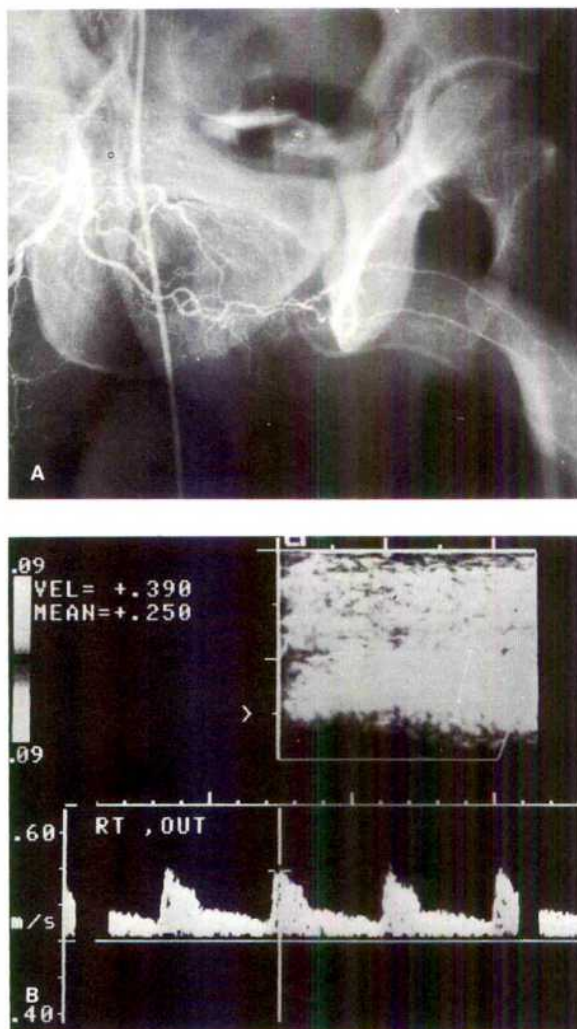


Fig. 2 A 59-year-old patient recently suffered from erectile dysfunction. Psychogenic impotence was diagnosed after a series of examinations. (A) The arteriogram shows good visualisation of the cavernosal artery. (B) The peak velocity after papaverine injection is 39 cm/s.

Table 6 Sensitivity, Specificity and Accuracy of Colour Duplex Sonography in the Assessment of Vascular Findings in Arteriograms

Sensitivity	$\frac{tp \times 100}{tp + fn} = \frac{14 \times 100}{14 + 3} = 82.4\%$
Specificity	$\frac{tn \times 100}{tn + fp} = \frac{7 \times 100}{7 + 0} = 100.0\%$
Accuracy	$\frac{tp + tn}{total} = \frac{14 + 7}{24} = 87.5\%$

Discussion

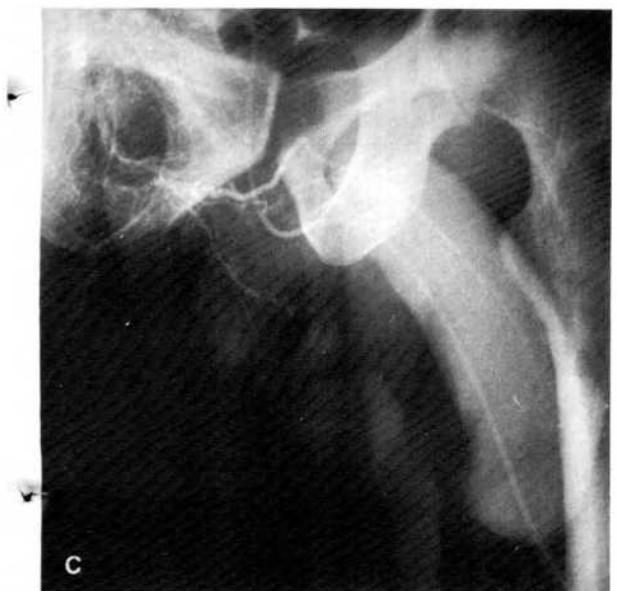
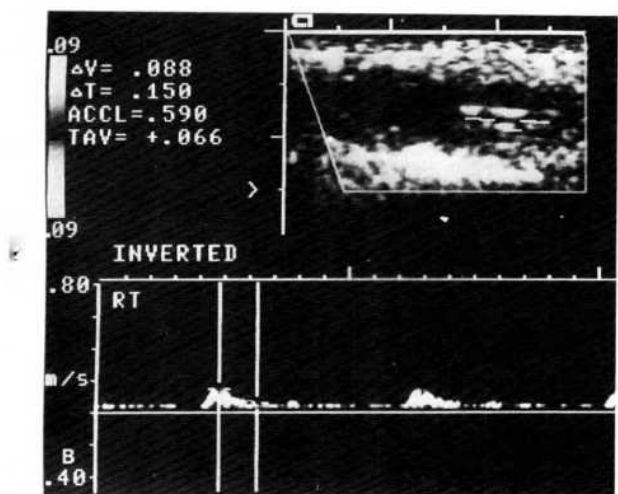
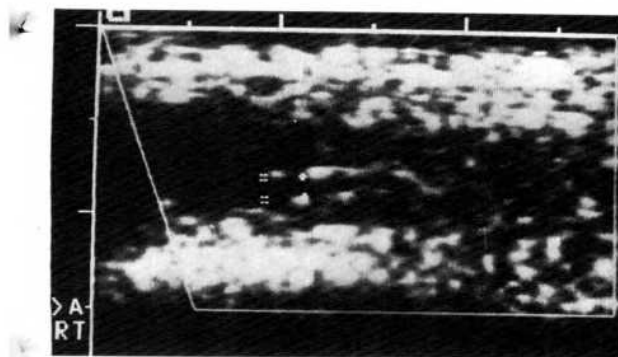
Recent advances in the understanding of erectile physiology and pathophysiology as well as the technological development of reliable diagnostic procedures have allowed the intensive investigation of impotence.

The use of intracorporeal injection of papaverine indicated that it might be a useful test in the assessment of vasculogenic impotence (Virag *et al.*, 1984). Lue *et al.* (1985) analysed the anatomy and physiology of vasculogenic impotence by combining intracorporeal papaverine injection with duplex sonography. The procedure was time-consuming and tedious owing to the difficulty of localisation of the cavernosal arteries and stabilisation of the sample volume (Collins *et al.*, 1987). When the high cost of the equipment is also taken into account, general acceptance of the test has been limited (Melman, 1988).

However, the use of colour duplex sonography could improve the shortcomings associated with conventional duplex sonography. The identification of the cavernosal artery, measurement of diameter and calculation of velocity were always completed within 1 min. Several of our patients reached the cavernosal artery peak velocity 1 min after removal of the rubber band. Thereafter, the peak velocity might have been underestimated using conventional duplex sonography.

The results indicate that the cavernosal artery peak velocity is a useful indicator of erectile function. The diameter of the cavernosal artery before papaverine injection in poor responders seemed to be greater than in good responders (Table 2). This might be due to arteriosclerotic changes in the poor responders, although the statistical analysis (Wilcoxon rank sum test) exhibited significant ($P < 0.05$) variance in each erection grade (1 v 2, 3 v 1) (Table 2). The standard deviation was too large and the overlappings among each grade were obvious. Thus the predictive power of percentage increase in diameter was not as useful as peak velocity. A combination of a good percentage increase in diameter and poor peak velocity could suggest occlusion of the cavernosal artery (Fig. 3).

Comparative examinations using selective arteriography showed a high degree of correlation with colour duplex sonography (87.5%). There were 3 cavernosal arteries with good peak velocities (38, 41, 42 cm/s respectively) and non-visualisation of cavernosal arteries in arteriograms (false negatives). This might have been due to rapid erection with full rigidity and compression of the arteries



leading to poor visualisation of cavernosal arteries (Bahren *et al.*, 1988).

The specificity could reach 100.0%. In other words, no cavernosal artery would be visualised in the arteriogram if the peak velocity was below 25 cm/s. Our findings are similar to those of Bahren *et al.* (1988) and Jevtich (1984). They also observed agreement between Doppler and arteriography in the detection of obstructive vascular changes in about 90% of their patients. It has been suggested that compromised arterial inflow may be responsible for poor venous tone (Bookstein *et al.*, 1987). The results of venous ligation are only valid, however, in patients with normal arterial inflow (Wespes and Schulman, 1985). It is more logical to use cavernosography and cavernosometry with colour duplex as evidence of good cavernosal artery flow and poor clinical erection.

The colour duplex sonography equipment is expensive but can also be used in cardiovascular and gynaecological fields. It provides fast, reliable and non-invasive assessment of the penile vascular reaction during erection. The flow chart for the direction of further evaluation and treatment of impotence is suggested in Figure 4. Colour duplex sonography in combination with the papaverine test could be the cornerstone of this flow chart.

Fig. 3 A 37-year-old patient with primary erectile dysfunction. The diameter of the cavernosal artery measured 0.3 mm in the flaccid state. (A) The diameter measured 1.3 mm after the papaverine injection. (B) The peak velocity of the cavernosal artery after the papaverine injection is 13 cm/s. (C) The arteriogram shows occlusion of the cavernosal artery. Revascularisation with inferior epigastric artery anastomosed to dorsal artery (side-to-side) and corpus cavernosum was performed. A good result was noted after the operation.

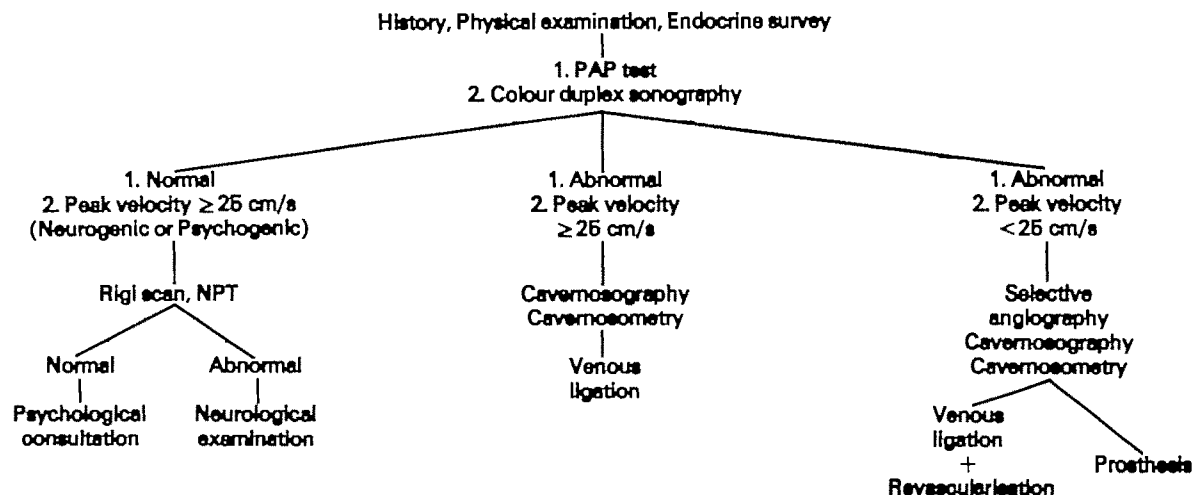


Fig. 4 Flow chart for the evaluation and treatment of impotent patients.

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Lord's Procedure—the Best Operation for Hydrocele?

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Summary—A prospective study was carried out to compare Lord's hydrocele operation with traditional surgical procedures. The groups of patients investigated were comparable in terms of age, period of observation, number of previous aspirations and size of hydrocele.

The incidence of isolated hydrocele of the spermatic cord, as well as epididymal cysts, was lower in the patients who underwent Lord's procedure (7.2 versus 15.8%), as was the percentage of patients reporting post-operative pain for more than 3 days (4.3 versus 15.8%, $p < 0.05$).

Hydrocele has long been a challenging subject. In 1964, Lord introduced a method which solved most of the problems associated with previously used techniques. While Lord's procedure is widely used in the English-speaking world, it is largely unknown in German-speaking countries. We have employed the eversion method of Winkelmann (1898), but the results were disappointing and this led us to apply Lord's procedure and compare it with traditional methods.

Patients and Methods

We performed a prospective study to compare Lord's hydrocele operation with other procedures in a controlled trial. Of 161 patients who underwent surgery for hydrocele between 1985 and 1988, 12 could not attend the follow-up examination. Of the remaining 149 patients, 113 (75.8%) were followed up by an investigator who had no detailed information concerning the patients at the time of examination. A total of 127 hydroceles were treated; 59 patients underwent Lord's procedure and 54 were treated by Winkelmann's method (Winkelmann, 1898). The surgeon assigned patients randomly to either group. Both groups were comparable in terms of age, period of observation, number of previous aspirations and size of hydrocele (Table 1).

Table 1 Details of Patients

	Lord's procedure	Control group
No. of patients	59	54
No. of operations	70	57
Median age (years) (range)	51.3 (17–81)	52.9 (16–80)
Median follow-up (months) (range)	22.2 (2–44)	25.6 (2–47)
Pre-operative aspirations	27.1%	27.8%
Large (> 100 ml)	18.6%	17.5%

Statistical evaluation was performed using the chi-squared test.

We modified Lord's method by selecting an approach through the raphe of the scrotum, since no major vessels are encountered in this area (Wright, 1966). A 3–4 cm incision was made, the hydrocele opened *in situ* and emptied (Fig. 1). The testis was extruded, turning the hydrocele sac inside out; 8 to 12 gathering sutures (plain catgut 4 × 10) were inserted at 1-cm intervals from the cut edge of the tunica vaginalis to the epididymis without suturing the latter (Fig. 2). The sutures were not tied until the final one had been placed. The tunica then lay gathered in a collar-like fashion around the testis (Fig. 3). The testis was replaced and the scrotum closed in 2 layers without drainage.

Results

The post-operative course was uncomplicated in

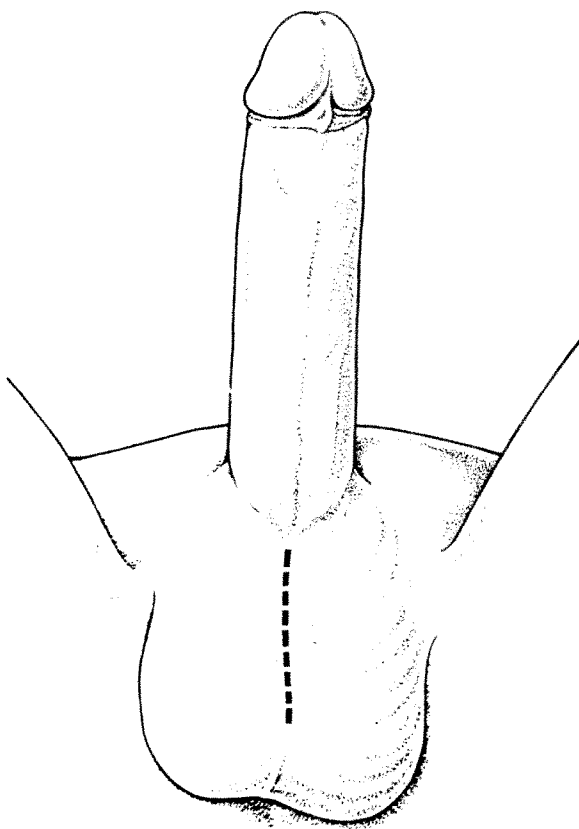


Fig. 1 Site of incision.

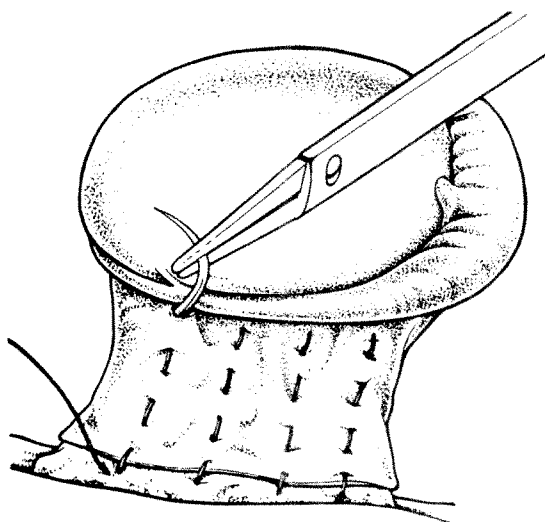


Fig. 2 Gathering sutures.

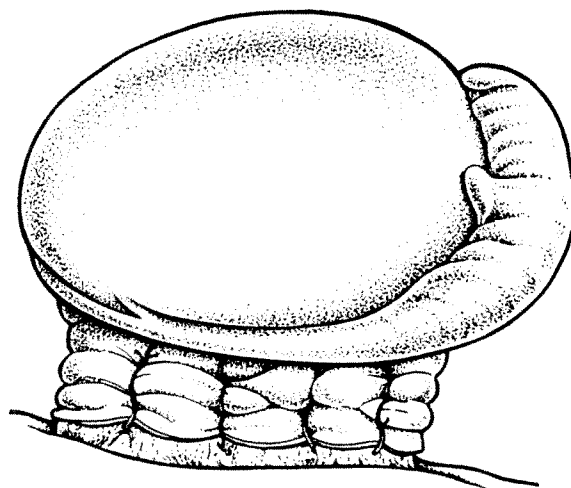


Fig. 3 Tunica vaginalis lying around the testis.

90% of patients (controls 77.2%). The number who reported post-operative pain for more than 3 days was significantly lower (4.3%) in the group who underwent Lord's procedure, compared with 15.8% in the control group (Table 2). The average duration of post-operative hospitalisation was 2.2 days for the Lord's group and 2.8 days for the controls. The results of surgery were excellent in 77.1% (controls 63.2%) and satisfactory in an additional 10% (controls 10.5%). In 12.9% of patients the results were poor (controls 24.6%), with an incidence of isolated hydrocele of the spermatic cord and epididymal cysts of 7.2% (controls 15.8%) (Table 3).

In the control group, massive haematoma occurred in 2 patients and required surgery. Thus no residual haematoma is reported in this group. We classified pathological findings after palpation of the scrotum but regarded an inconspicuous scar as normal (Table 4).

Discussion

Surgical correction of hydrocele is among the oldest surgical techniques and was described in the first century A.D. by Celsus. In 1967, Landes and Leonhard reviewed the procedures employed over the years. In the fifteenth century the hydrocele was removed together with the testis (Heister, 1763). Injection of various substances (mainly phenol) was common. Although Tait (1913) and Young (1940) considered these methods to be dangerous and ineffective, they continue to be documented in current publications (Bodker *et al.*, 1985; Hellström *et al.*, 1988).

Table 2 Complications

	Lord's procedure (%)	Control group (%)
No. of operations	70	57
No. complications	63 (90.0)	44 (77.2)
Haematoma	2 (2.9)	2 (3.5)
Epididymitis	1 (1.4)	—
Wound problem	1 (1.4)	2 (3.5)
Pain > 3 days	3 (4.3)	9 (15.8) $P < 0.05$

Table 3 Results of Operation (Major Changes)

	Lord's procedure (%)	Control group (%)
No. of operations	70	57
Recurrences	3 (4.3)	3 (5.3)
Oedema	1 (1.4)	2 (3.5)
Funicular hydrocele + epididymal cyst	5 (7.2)	9 (15.8)

Table 4 Minimal Palpable Changes

	Lord's procedure (%)	Control group (%)
No. of operations	70	57
Tunica vaginalis	4 (5.7)	4 (7.0)
Thickened epididymis	1 (1.5)	2 (3.5)
Residual haematoma	2 (2.9)	—
No changes	54 (77.1)	37 (63.2)

Currently, the most popular techniques are complete excision (Young, 1940) or eversion of the tunica vaginalis (Wilkinson, 1973). In the English-speaking world several methods have been developed which empty the hydrocele with minimal dissection of the tunica vaginalis (Solomon, 1955; Lord, 1964, 1972). The incidence of haematoma associated with both excision and eversion ranges from 20 to 30% and the infection rate from 8 to 26% (Dahl *et al.*, 1972).

Many reports (Haas *et al.*, 1978; Waldron *et al.*, 1986; Kollwitz *et al.*, 1988) demonstrate the superiority of Lord's procedure. In this study we have demonstrated that it is safe, reliable and yields optimum results. Its major benefits include a shorter period of post-operative pain and a lower incidence of recurrence. Since a short incision is sufficient to empty the hydrocele sac, the cosmetic result is markedly superior. The approach via the raphe of

the scrotum permits bilateral procedures with one incision. We recommend Lord's procedure as the treatment of choice for all types of hydrocele.

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Stage I Seminoma of the Testis. Adjuvant Radiotherapy or Surveillance?

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Summary—Lately the role of radiotherapy in stage I seminoma of the testis has been questioned by some authors who reported on a "surveillance" strategy for these patients. Since 1980, 124 patients with seminoma of the testis have been referred to this institution; 97 of 116 patients analysed presented with stage I disease and 10 of these had elevated levels of β HCG.

A total of 64 patients were given radiotherapy after orchiectomy and 33 entered a surveillance protocol. After a median follow-up of 48 months, 3 patients in the surveillance group relapsed after 5, 13 and 49 months and 2 of the irradiated patients did so after 25 and 33 months. Elevation of β HCG was not significant because none of these patients showed progression.

A low rate of progression and excellent survival are associated with standard treatment (orchiectomy and radiotherapy) and good results have been achieved with chemotherapy in cases of relapse. A surveillance policy is not recommended in stage I seminoma because of its slower growth compared with non-seminomatous germ cell tumours (NSGCT), the absence of a specific tumour marker, the 10% risk of occult metastases and the 3-fold higher progression rate compared with irradiated patients. We suggest the use of a reduced dosage and radiation field.

Testicular seminoma has proved to be extremely responsive to therapy. After standard therapy—infra-diaphragmatic lymph node irradiation—excellent cure rates have been reported, with survival rates of 85 to 90% in stage I tumours (Thomas *et al.*, 1982; Peckham 1988; Fossa *et al.*, 1989). In view of the low rate of occult metastases (in approximately 10% of cases) (Maier *et al.*, 1968) and the morbidity of radiation therapy (impaired spermatogenesis, peptic ulceration, bowel complications and second malignancies) (Hay *et al.*, 1984; Hamilton *et al.*, 1987; Coia and Hanks, 1988), it has been suggested that radiotherapy should be omitted.

To find out if it is possible to reduce therapy without compromising patients' safety, we evaluated the follow-up of patients with seminoma stage I who were treated either with adjuvant radiotherapy or surveillance after orchiectomy between 1980 and 1988 at Hannover Medical School.

Patients and Methods

Since 1980, 124 patients with seminoma of the testis have been referred to this institution. Eight patients were lost to follow-up; 7 of these had stage I tumours—6 in the radiotherapy group and 1 in the surveillance group. Of the remaining 116 patients, 97 (83.6%) presented with stage I disease and thus could be analysed; 10 of these (10.5%) had elevated levels of β HCG. Sixty-four patients were given radiotherapy after orchiectomy and 33 were assigned to a surveillance protocol. The decision on treatment was made by the patient himself after being fully informed of the advantages and disadvantages of both strategies. The median ages of 32.5 years (range 18–67) in one group and 33 years (range 21–48) in the other group were comparable.

Stage I seminoma was defined by (1) verification of a histologically pure seminoma, (2) β HCG in the normal range or decreasing after orchiectomy (patients with elevated levels of alpha-fetoprotein (AFP) were treated as having non-seminomas) and (3) ultrasonography of the abdomen, CT of abdo-

men and chest and conventional chest X-ray without evidence of tumour spread.

Patients in the surveillance group were followed up closely with monthly examinations (AFP and β HCG, chest X-ray and either CT scan or sonography) in the first year, 2-monthly in the second year and every 3 months in the third to fifth years. Irradiated patients were followed-up every 3 months for the first 2 years and every 6 months for the third and fourth years, with annual visits thereafter.

Results

In all, 97 patients were followed up for a median of 48 months (range 4–110) and 5 patients (5.2%) relapsed; 3 (9.1%) of the 33 patients in the surveillance group showed progression after 5, 13 and 49 months and 2 of the irradiated patients (3.1%) did so after 25 and 33 months (Table 1). Details of relapse and treatment are summarised in Table 2. Of the 2 relapsing patients in the irradiated group, 1 developed isolated lung metastases and was treated with 4 cycles of chemotherapy (cisplatin vinblastine, bleomycin—PVB) and resection of

residual tumour. He has been disease-free for 65 months. The other patient, who had a prior herniorrhaphy, showed progression in the irradiated area, retroperitoneal and inguinal. He received 2 cycles of PVB and secondary retroperitoneal lymph node dissection (RPLND) and has been disease-free for 46 months. All of the 3 relapsing patients in the surveillance group showed retroperitoneal progression and were cured by different types of therapy; carboplatin and secondary RPLND and radiation or chemotherapy alone. No patient has died from his disease or from complications of treatment.

Ten of the 97 patients (10.5%) had elevated levels of β HCG prior to orchiectomy; 6 of them received adjuvant radiation therapy and 4 were entered into the surveillance protocol; none relapsed.

Histopathologically we found 95 cases of classical seminoma, 1 anaplastic and 1 spermatocytic seminoma.

Relapse occurred in 3% of patients with pT1 tumours, 7% with pT2 and 17% with pT3 lesions (Table 3). To ascertain if there was a rise in relapse probability with increasing pT stage the trend test (Armitage, 1955) was applied (using the StatXact package (Mehta *et al.*, 1988; Gajjar *et al.*, 1989). The exact one-sided *P* value for the observed trend was 0.08, so that the correlation was significant on the level of 10% but not 5%.

Delay in presentation was assessed in 67/97 patients, with 3 of these relapsing. The latter subgroup showed a preference for longer intervals (median 26 weeks) compared to the patients with no evidence of disease (NED) (median 3 weeks). The difference was statistically significant (log rank test, one-sided *P* value = 0.0387) (Kalbfleisch and Prentice, 1980).

Four patients (4.1%) developed a secondary malignancy after 14, 16, 72 and 84 months: in 1 a

Table 1 Surveillance versus Adjuvant Radiotherapy

Surveillance	Radiotherapy
No. = 33	No. = 64
NED 30	NED 62
Relapse 3 (9%)	Relapse 2 (3%)
Therapy	Therapy
NED 3	NED 2

NED = No evidence of disease.

Table 2 Details of Relapse

No. of patients	Radiotherapy	Time to relapse (months)	Sites of relapse	Treatment	Status (months)
1	Yes	33	Retroperitoneal/inguinal	PVB + RPLND	NED 46
2	Yes	25	Pulmonary	PVB + L-Op	NED 65
3	No	49	Retroperitoneal	CP + RPLND	NED 33
4	No	5	Retroperitoneal	RPLND + RT	NED 43
5	No	13	Retroperitoneal/cervical	Cisplatin	NED 28

PVB = Cisplatin, vinblastine, bleomycin.

CP = Carboplatin.

RPLND = Retroperitoneal lymph node dissection.

L-Op = Resection of residual pulmonary tumour.

RT = Radiotherapy.

NED = No evidence of disease.

Table 3 pT Stage

pT	No. of patients (%)	Relapses (%)
1	64	2 (3)
2	27	2 (7)
3	6	1 (17)

seminoma and in 3 a non-seminomatous germ cell tumour of the contralateral testis.

Discussion

Many patients with seminoma of the testis have stage I disease at presentation, with percentages ranging between 69 and 84% (Calman *et al.*, 1979; Thomas *et al.*, 1982; Krag-Jacobsen *et al.*, 1984; Babaian and Zagars, 1988; Ellerbroek *et al.*, 1988). In the present study, 83.6% presented with stage I disease, which would seem to indicate a low metastatic potential. The historical data of Maier *et al.* (1968) showed a 10% incidence of occult metastases in patients presenting with stage I seminoma, but the methods of staging at that time were unsatisfactory and the more precise imaging systems used today may mean that the rate of occult metastases is even lower.

Excellent survival and low relapse rates have been reported in patients with seminoma of the testis stage I after orchiectomy and adjuvant radiotherapy (Table 4). Furthermore, there is effective salvage treatment for patients who relapse (Thomas *et al.*, 1982; Loehrer *et al.*, 1987).

Table 4 Relapse Rates after Orchiectomy and Adjuvant Radiotherapy

	No. of patients	No. of relapses	Rate (%)
Ball <i>et al.</i> (1982)	232	4	3.0
Fossa <i>et al.</i> (1989)	365	13	3.5
Hamilton <i>et al.</i> (1986)	232	5	2.0
Thomas (1985)	150	2	1.0
Zagars (1988)	163	7	4.2

Table 5 Relapse Rates after Surveillance

	No. of patients	Follow-up (months) Median (range)	Relapse	Rate (%)	Time (months) Median (range)
Horwich and Peckham (1988)	90	18 (4-40)	10	11.0	11 (7-24)
Peckham <i>et al.</i> (1987)	52	23 (12-41)	7	13.4	11 (6-23)
Thomas <i>et al.</i> (1989)	81	19 (3-43)	3	3.7	5 (3-18)
Present series	33	48 (4-110)	3	9.1	13 (5-51)

Successful results of a surveillance policy for stage I non-seminomatous germ cell tumours of the testis were reported by Peckham *et al.* (1982) and this raised the possibility of adopting a similar approach to stage I seminomas to avoid unnecessary additional therapy. Some initial results of the "wait and see" policy in testicular seminoma stage I revealed relapse rates of 3.7 to 13.4%, but follow-up was relatively short (Table 5).

Our relapse rate of 3.1% after adjuvant radiotherapy is similar to that of other series (Table 4). Patients in the surveillance group showed progression in 9.1%, thus recording a relapse rate 3 times higher than that of irradiated patients. This includes 1 patient with progression after 49 months and underlines the possibility of late recurrence in this group, as already described by other authors. Ellerbroek *et al.* (1988) reported a 30% relapse rate after 3 years, Calman *et al.* (1979) reported recurrence after 6 years, and Warhol *et al.* (1983) after 17 years.

Elevation of serum β HCG is described in 10 to 21% of seminoma patients (Mann and Siddle, 1988), whereas morphological correlation (syncytiotrophoblastic cells) could be established in only 4 to 14.5% (Butcher *et al.*, 1985). Javadpour (1986) suggested a worse prognosis for patients with β HCG-positive seminoma, but the results in our study (no relapse in 10 patients with elevated levels of β HCG) corroborate the experience of other authors (Peckham *et al.*, 1987; Babaian and Zagars, 1988; Wilkinson *et al.*, 1988). Thus we would not recommend a change from the usual policy for these patients.

The side effects of adjuvant radiotherapy are relatively infrequent and usually affect the gastrointestinal tract (Peckham, 1988; Fossa *et al.*, 1989). Coia and Hanks (1988) reported about 4% of patients with severe complications requiring hospitalisation in a series of 883 patients who received radiotherapy for seminoma or Hodgkin's disease. With dosages below 35 Gy, Prosnitz (1988) observed only 1% of patients with major complications. The risk of infertility presents a special problem (Thomas *et al.*, 1977). Even with careful

scrotal shielding, either oligozoospermia or azoospermia persists in approximately 50% of irradiated men. However, it should be remembered that 22 to 53% (Jewett and Jarvi, 1986) of all men after unilateral orchiectomy and before further therapy exhibit azoospermia and 25% of all patients with testicular tumours remain subfertile, regardless of therapy. On the other hand, the recovery of spermatogenesis after radiation therapy is possible.

The problem of second malignancies after radiotherapy has not yet been solved. Evaluation of the South Thames Cancer Registry for the period 1961 to 1980 by Coleman *et al.* (1987) did not reveal an excessive incidence of second cancers among men with testicular cancer, apart from contralateral testicular neoplasms. For the latter the risk rose from 2.9 to 14.3 over the 2 decades, with relatively few men being treated by chemotherapy alone in either time period. Kaldor *et al.* (1987) reported a 2-fold higher chance of developing second malignancies in testicular cancer, but the study did not allow any differentiation with respect to the therapeutic approach previously selected. Hamilton *et al.* (1986) suggested that there was no increased risk compared with the normal population, but Hay *et al.* (1984) found a 9% incidence of second, non-testicular malignancies in patients irradiated between 1950 and 1969. Fossa *et al.* (1989) observed a 2-fold higher chance of developing second malignancies compared with the general population, though in this series tumours of the contralateral testis were included.

A relapse rate of 9 to 13% in a surveillance policy seems to be acceptable, even in comparison with 20 to 30% in NSGCT stage I. However, the time to relapse is usually longer than in NSGCT and it must be remembered that the follow-up in previous studies was relatively short. Furthermore, relapse is confined in most cases to the retroperitoneum, which is a more difficult area to assess by imaging techniques. Though all relapses have been salvaged, surveillance in seminoma patients might be considered more complicated and costly because a longer period of intensive follow-up is required. In addition, a satisfactory serum tumour marker has yet to be discovered. Placental alkaline phosphatase (PLAP) has been thought to be of value (Horwich *et al.*, 1985), but observations of elevated levels of PLAP in 55 to 90% of seminoma patients with active disease (Horwich *et al.*, 1985) would indicate a sensitivity lower than that required for reliable follow-up.

The difference between 3.1% and 9.1% in irradiated and surveillance patients does not attain

statistical significance, but in calculating the low number of overall relapses, about 20 000 probands are necessary to detect the proposed difference as significant with a power of 95% (Sachs, 1982). In spite of this, the 3-fold higher relapse rate must be emphasised, and so in our opinion radiotherapy remains an important and safe method of treatment for patients with seminoma stage I.

A more vexing question is whether dosage and radiation field can be optimised. Total dosage should not exceed 30 Gy (Hanks *et al.*, 1981) and satisfactory results have been obtained even with 25 Gy (Thomas, 1985). Fossa *et al.* (1989) require that the inguinal region be excluded even in patients with a past history of inguinal or scrotal surgery. Radiation of the ipsilateral iliac region may also be questioned, since iliac tumour growth is rare in patients with testicular cancer (Fossa *et al.*, 1989). Considering these restrictions, immediate and long-term morbidity can probably be reduced even further.

Another option seems to be the use of carboplatin: it has been established that seminoma, as well as being more radiosensitive than non-seminoma, is also more chemosensitive. This has been reflected by the observation that approximately 70% of patients can become disease-free with cisplatin alone (Oliver, 1987), compared with 10% of patients with NSGCT (Higby *et al.*, 1974). Two courses of adjuvant treatment provide a realistic alternative to radiotherapy and may well be less toxic (Peckham *et al.*, 1985; Oliver, 1987). It is probable that a prospective study comparing radiotherapy and carboplatin may be indicated in stage I seminoma.

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PAEDIATRIC UROLOGY

Clinical Patterns of Paediatric Urolithiasis

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Summary—A series of 270 paediatric stone patients was studied retrospectively according to the clinical pattern of urolithiasis (age and sex, stone location, stone analysis, recurrence rate) and aetiology of stone disease (infection, anatomical, metabolic or idiopathic). Infection stones occurred earliest and more commonly in males and were usually upper tract struvite calculi related to *Proteus* infection. Anatomical stones were most commonly associated with pelviureteric junction (PUJ) obstruction and had a high recurrence rate, despite surgical correction of obstruction. Idiopathic stones most resembled those found in adult urolithiasis by virtue of occurring latest, being sited in the ureter more often and being more frequently composed of calcium oxalate. Metabolic stones were most frequently calcium phosphate or cystine and virtually all were renal. They comprised the smallest group but had the highest recurrence rate.

Paediatric urolithiasis is uncommon and exhibits distinct geographic variability with regard to stone aetiology. The objective of this study was to investigate a large series of paediatric stone formers and to classify them according to aetiology of stone formation—infection, idiopathic, anatomical and metabolic. The clinical patterns of stone disease were then examined within each aetiological category in terms of age, anatomical location, chemical analysis and recurrence rate.

Patients and Methods

A retrospective study was carried out on 270 consecutive children with a diagnosis of urolithiasis, admitted to this hospital between January 1958 and June 1985. There were 182 boys (68%) and 88 girls (32%), whose ages ranged from 4 months to 16 years (mean 5.2 for boys and 6.9 for girls).

Routine radiographic imaging entailed an intravenous urogram (IVU) or ultrasound study. Voiding cystourethrograms were performed in children with infection to rule out vesicoureteric reflux.

In 227 patients (84%) chemical analysis was performed after removal or passage of the stone. A metabolic evaluation was carried out on 189 children and included tests for serum electrolytes, calcium, phosphorus, uric acid and oxalate; an ammonium chloride loading test; a 24-h urine collection for calcium, phosphorus, uric acid and a sodium nitroprusside test for cystine. Urine specimens were sent for culture upon initial presentation and urinary tract infection (UTI) was defined as a culture growing $> 10^5$ organisms per ml.

The retrospective evaluation classified patients with urinary tract stones into 4 groups: infection, anatomical, idiopathic or metabolic and took into account the stone composition, location and recurrence rate.

An infection stone was defined as being associated with a urine culture growing $> 10^5$ organisms per ml and chemical stone analysis consistent with struvite, calcium apatite or mixed stones. An idiopathic stone was one that had no discernible aetiology with the exception of hypercalciuria or recumbency. An anatomical stone was defined as being associated with a hydronephrotic collecting system, suggestive of stasis, without evidence of urinary infection. A metabolic stone was one that was associated with predisposing metabolic disease but unassociated with infection or an anatomical lesion.

Results

Infection

Of 270 patients, 161 (60%) had infection-related stones. The male to female ratio was 2:1. The mean age for infection stone formation was 4.9 years (range 4 months–15 years). Two-thirds of the patients were 5 years of age or less (Fig. 1). The vast majority of infection stones occurring before the age of 2 were in males.

Infection stones were predominantly renal in location (70%) (Fig. 2); 13% were ureteric and 17% were located in the bladder or urethra. In 26 patients (16%) infection stones presented bilaterally.

Proteus was the predominant predisposing organism, accounting for 82% of positive urine cultures with pure growth. *E. coli* was the second most common pathogen, responsible for 9% of pure urine cultures; 25% of urine cultures were mixed growth, with a combination of *Proteus* and *E. coli* accounting for 63%.

Chemical stone analysis indicated that 72% of infection stones were struvite; 11% of stones were calcium phosphate and 17% were mixed.

One-third of patients were found to have anatomical lesions which were felt to contribute to infection stone formation. Amongst the renal stone formers the common anomalies were pelviureteric junction obstruction (8%), primary obstructed megaureter (7%) and neuropathic bladder (4%). Amongst bladder stone patients, exstrophy and epispadias accounted for 3%.

All patients with UTI received antibiotic therapy in hospital and those with infection stones had prophylactic antibiotics for an average of 2 years.

In 22 patients, infection stones recurred following initial management (recurrence rate 14%). The median interval to recurrence was 1 year (mean 4 years, range 4 months–13 years).

Idiopathic

Seventy-three patients (27%) were idiopathic stone formers. Their mean age at presentation was 8.4 years (range 2–17 years) (Fig. 1).

While the majority of idiopathic stones were renal in location (58%), a large percentage were ureteric (29%). Chemical analysis showed a fairly even distribution between struvite (29%), calcium

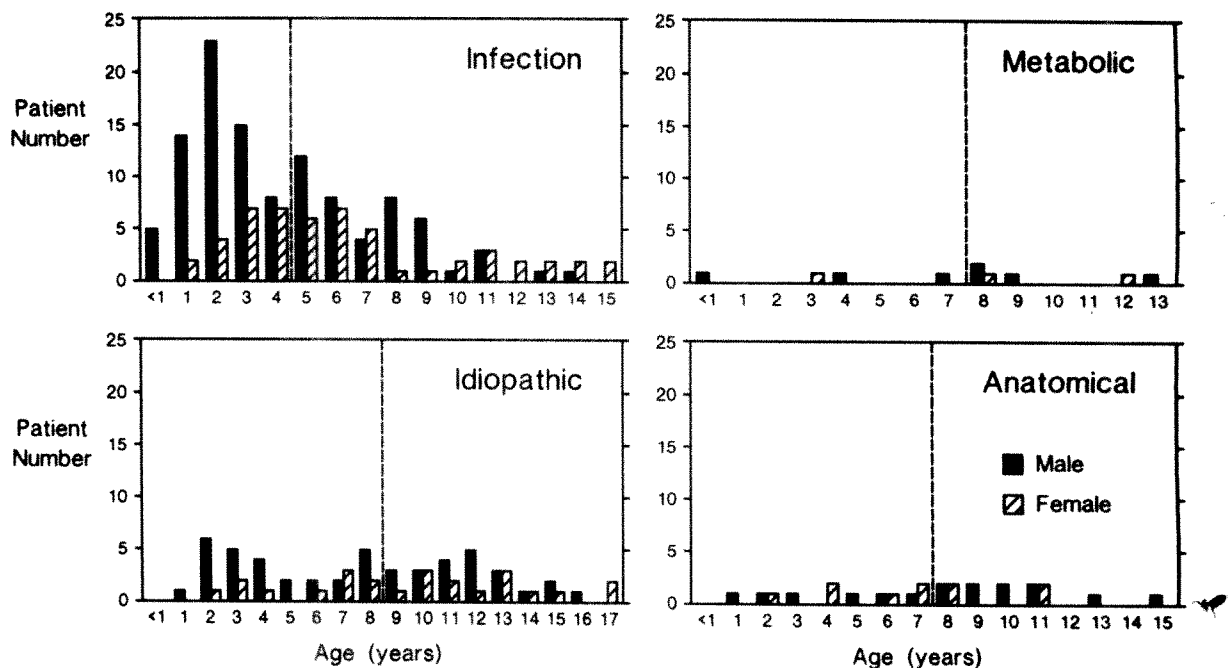


Fig. 1 Stone presentation in each aetiological category according to age and sex.



Fig. 2 Bilateral struvite calculi in 5-year-old female with *Proteus* urinary tract infection and non-functioning right kidney.

oxalate (19%) and mixed stones (16%). Hypercalciuria (defined in this group as $>6\text{mg/kg/day}$ calcium excretion) was noted in 16% of idiopathic stone formers. In 10 of 12 patients, the hypercalciuria was transient. Recumbency as a result of head injuries or orthopaedic problems accounted for 7% of idiopathic stones.

The idiopathic stone recurrence rate was 14%, identical to that of infection stone formers. The median interval to recurrence was 15 months (mean 3 years, range 2 months–10 years).

Anatomical

Ten per cent of patients were anatomical stone formers. Their mean age was 7.5 years (range 1–15 years) (Fig. 1). The vast majority of anatomical stones were renal (77%). Only 8% were ureteric and 15% were lower tract calculi. Chemical analysis showed an even distribution of calcium phosphate, struvite and mixed stones. Pelviureteric junction obstruction accounted for the majority (54%) of upper tract anatomical stones, with primary obstructed megaureter being the second most common lesion. Among lower tract anatomical stone formers, bladder neck reconstruction was the most common predisposing factor.

The rate of anatomical stone recurrence (27%) was virtually twice that of infection and idiopathic stones. The median interval to recurrence was 2 years (mean 4 years, range 17 months–12 years).

Persistent hydronephrosis was present in all patients with anatomical stone recurrences.

Metabolic

The 10 metabolic stone formers comprised the smallest group of patients (3%). Their mean age at presentation was 7.3 years (range 11 months–13 years). Metabolic stones were virtually all renal in location (90%), with no ureteric stones, and only one occurring in the bladder. Calcium phosphate was the most common type of metabolic stone (60%), with cystine stones occurring in 20% of cases. Renal tubular acidosis and mild decreases in urinary acidification were documented in 70% of metabolic stone formers. Three patients with cystinuria (30%) made up the remainder of the metabolic stone formers.

The metabolic stone recurrence rate of 30% was the highest of the 4 groups. The median interval to recurrence was 6 years (mean 6 years, range 2–7 years). Two of the 3 recurrences were in poorly controlled cystinurics.

Discussion

This is the first study of paediatric urolithiasis to evaluate the clinical presentation of stone disease according to stone aetiology, with particular reference to the distinct differences among infection, anatomical, metabolic and idiopathic stone formers.

In keeping with other United Kingdom stone series, infection stones predominated, accounting for 60% of this particular series. This figure is intermediate between the 29% infection stone rate reported by Gaches from Bristol (United Kingdom) and the 82% reported by Ghazali from the United Kingdom and Ireland (Gaches *et al.*, 1975; Ghazali, 1975). Infection stones presented at a distinctly earlier age than the 3 other stone types; two-thirds of the patients were ≤ 5 years (mean = 4.9). The vast majority of infection calculi (83%) were located in the upper tract and in 16% of cases were bilateral. Vesicoureteric reflux was diagnosed in 12% of infection stone formers. This appeared to be related to struvite calculus formation in 3 exstrophy patients and in 2 patients with massive bilateral reflux. In the 15 remaining patients, however, the importance of the reflux as an aetiological factor in stone disease was questionable. In 4 patients with bladder calculi the reflux resolved following cystolithotomy. In 6 of the renal stone patients the reflux resolved following stone clearance and sterilisation of urine.

The second largest group of patients were the idiopathic stone formers (27%). Of all the paediatric stone formers studied, the idiopathic group presented at the latest age and most resembled adult stone patients in their clinical presentation. These patients were more likely than any other group to present with a ureteric stone. In accordance with the high incidence of calcium oxalate stones in this group, a significant percentage of these patients had hypercalciuria at the time of diagnosis. This was defined by Royer (1961) and confirmed in the Alder Hey population as a calcium excretion of ≥ 6 mg/kg/day. In 10 of our 12 patients the hypercalciuria was transient and thus considered to be an epiphenomenon of the stone disease (Johnston and McKendrick 1974).

Amongst the 10% of our patients who were anatomical stone formers, the majority had associated pelviureteric junction obstruction (54%). These patients were managed with combined pyelolithotomy and pyeloplasty, as an attempt was routinely made to correct any predisposing anatomical lesion at the time of stone removal. Anatomical stone formers were distinctive in that chemical analysis showed an even distribution of calcium phosphate, mixed and struvite stones; they also had a particularly high recurrence rate (27%). All recurrent anatomical stone formers had an element of hydronephrosis, in most cases despite surgical correction of an obstructing lesion (PUJ obstruction, primary obstructive megaureter). Definitive management of these patients entailed lower pole partial nephrectomy for poorly draining, dilated systems or nephrectomy for markedly atrophic kidneys.

As is the case in virtually all series of paediatric urolithiasis, metabolic stone formers comprised our smallest group of patients, with only 3% having a

clearly defined metabolic aetiology. Renal tubular acidification defects were most common, followed by cystinuria. We found 2 distinct clinical features among metabolic stone formers—the highest incidence of renal stones and no cases of ureteric stone. In addition, the recurrence rate among metabolic stone formers (30%) was the highest of all 4 groups. Because metabolic defects were diagnosed at initial presentation and appropriate medical therapy instituted, the high recurrence rate indicates the management challenge that these patients represent.

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Experience with the Fowler Stephens and Microvascular Procedures in the Management of Intra-abdominal Testes

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Summary—The Fowler Stephens operation and microvascular procedures were compared for the management of 23 intra-abdominal testes in 15 boys, 7 of whom had the prune belly syndrome. The Fowler Stephens operation was used for 15 testes (4 single-stage and 11 two-stage) and microvascular transfer was used for 8 testes. Eleven testes treated by the Fowler Stephens procedure (73%) and 7 treated by microvascular procedures (88%) were viable and intrascrotal after an average follow-up of 3.0 years, giving an overall success rate of 78%. Eight of 9 post-pubertal testes were biopsied. Severe maturational arrest was evident in all and carcinoma *in situ* was present in one.

Specialised orchiopexy procedures may be indicated for cases of bilateral intra-abdominal testes, or when a solitary testis is located in the abdomen. There have been relatively few reasonably sized studies reporting a long-term follow-up after the Fowler Stephens procedure or after microvascular transfer of intra-abdominal testes. We report a retrospective study of 15 boys with 23 intra-abdominal testes and compare the Fowler Stephens procedure with microvascular free transfer in the management of intra-abdominal testes.

Patients and Methods

Between August 1982 and February 1990 either the Fowler Stephens operation or microvascular transfer was used in 15 boys (age range 3–18 years, mean 12.1) for the management of 23 intra-abdominal testes. Of the 7 other testes, 1 was normally situated in the scrotum, 3 were intracanalicular and have undergone pre-peritoneal or routine orchiopexy; the other 3 were intra-abdominal but have been

excluded from this study because 1 was treated by a Fowler Stephens operation by another surgeon, 1 is waiting for a Fowler Stephens operation, and 1 was removed at the time of renal transplantation.

Among the 15 boys there were 2 groups of patients. Seven boys had the prune belly syndrome, all with bilateral intra-abdominal testes, 12 of which are included in this study, and the mean age at first operation was 12.4 years.

The second group included 8 boys without the syndrome, 4 with bilateral intra-abdominal testes; 11 testes were included in this study and the patients' mean age at first operation was 6.5 years.

Patients in the first group were presumed to have bilateral intra-abdominal testes as part of their prune belly syndrome. In the second group 6 boys underwent preliminary laparoscopic evaluation and 1 had a groin exploration to confirm the presence of an intra-abdominal testis. The eighth boy in this group had had previous bilateral orchiopexies for bilateral intra-abdominal testes, at which the testes had only been brought into the inguinal canals.

Of the 15 boys, 6 were operated on after puberty and 6 had an HCG stimulation test.

The Fowler Stephens operation was used for 15

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testes. The mean age of boys undergoing 4 single-stage Fowler Stephens procedures was 4.75 years and the mean age at first operation in the 11 2-stage procedures was 11.2 years, giving an overall mean age at first operation of 10.2 years. The time interval in the 2-stage procedure was 4 to 12 months (mean 7.3).

Eight microvascular transfers were performed, with a mean age at operation of 8.5 years.

A Prader orchimeter was used to gauge the size of the testis, combined with a subjective opinion as to the consistency of the testis, in the post-operative assessment of both procedures, at a mean of 3.0 years. Eight of 9 post-pubertal testes were biopsied at operation.

Results

The Fowler Stephens operation was used in the management of 15 testes, with a follow-up of 1.5 to 5.75 years (mean 3.0). No testis atrophied following first-stage vessel ligation. Two of the 4 single-stage procedures were judged successful and 2 a failure. Nine of the 11 testes that had a 2-stage procedure were deemed successful and 2 failed. Thus 11 of the 15 testes (73%) treated by a Fowler Stephens procedure were viable and intrascrotal at a mean follow-up of 3.0 years.

Following 8 microvascular transfers of testes, with a follow-up of 6 months to 4.25 years (mean 3.0 years), the outcome was successful in 7 (88%).

The 7 boys with prune belly syndrome all had bilateral intra-abdominal testes. Five had their operation after puberty, 1 has developed secondary sexual characteristic changes after his operation, and the seventh boy is still pre-pubertal and has not had an HCG stimulation test.

Four of the 8 boys without prune belly syndrome also had bilateral intra-abdominal testes; 3 had a good response to HCG stimulation; the fourth is still pre-pubertal and did not have an HCG stimulation test. One of the remaining 4 boys had a normal scrotal contralateral testis and the other 3 had a contralateral conventional orchiopexy prior to the operation for their intra-abdominal testis—one has subsequently successfully developed secondary sexual characteristics and the other 2 had a good testosterone response to HCG stimulation.

Eight of the 9 post-pubertal testes were biopsied and all showed severe maturational arrest. One biopsy, in a 17-year-old prune belly syndrome boy, was thought to show "atypical" cells. When his contralateral intra-abdominal testis was removed at the time of renal transplantation, it was found to

contain a seminoma. The original biopsy was reviewed and the diagnosis revised to carcinoma *in situ*. This testis has subsequently been treated with radiotherapy.

Discussion

The management of the impalpable testis presents the surgeon with a number of problems. Firstly, there is a need to establish whether the testis is absent or whether it is impalpable by virtue of being located in the abdomen. In the case of the intra-abdominal testis the question then arises as to whether orchiectomy is indicated or whether it is justifiable to proceed to some form of specialised orchiopexy to place the gonad in the scrotum. Finally comes the choice of surgical procedure, which currently lies between the Fowler Stephens operation and microvascular transfer. In many ways it is this last question, relating to surgical procedure, which is the most straightforward to answer.

We have shown that Fowler Stephens orchiopexy and microvascular transfer can both be successful procedures in the management of intra-abdominal testes. There have been relatively few reasonably sized studies reporting a long-term follow-up after either procedure. Clatsworthy *et al.* (1972) reported a 75% success rate with 32 Fowler Stephens procedures, and Gibbons *et al.* (1979) reported 81% success with 27 procedures, both with an "up to 6-year" follow-up. O'Brien *et al.* (1983) reported 54% success following 11 microvascular procedures with a follow-up of 12 to 72 months, and Bianchi (1984) reported 80% success following 10 microvascular procedures with a follow up of 1 to 24 months. In the present series, although the numbers are small in the subgroups, the 2-stage Fowler Stephens procedure was significantly more successful than the single-stage (*cf.* 50% to 80%). Although this involves 2 operations, the total operative time and hospital stay is, on average, shorter than that for a microvascular procedure. In this unit a bilateral microvascular transfer of intra-abdominal testes has taken up to 9 h, whereas total time expended on a bilateral 2-stage Fowler Stephens procedure averaged 4.5 h. The hospital stay following Fowler Stephens procedures is usually 2 to 5 days, whereas following microvascular transfer it is 8 to 11 days. Maybe the real advantage of the microvascular technique is that there are 2 possible blood supplies to the testis—that through the anastomosis and secondly the vessels with the vas. Bianchi (1984) noted that a testis whose arterial anastomosis failed

was viable in the scrotum 9 months later, presumably supplied by the artery to the vas, *i.e.* a Fowler Stephens procedure.

One of the greatest difficulties in this study, as in others, is how to assess success, especially in the pre-pubertal testis. It is relatively easy to confirm atrophy of a testis by palpation, but assessment of the consistency of a testis, especially before puberty, is necessarily subjective. We used a Prader orchimeter to gauge the volume of the testis and a subjective recording of the consistency of the testis to assess the post-operative outcome. There is a minimal increase in the volume of the testis up to 11 years of age and then there is a period of active growth with wide variation within the normal range (Schonfeld, 1943; Zilka and Laron, 1969). The volumes of the pre- and post-pubertal testes whose operative outcome was judged to be successful fell within this normal range.

Until recently it was often difficult to establish whether an impalpable testis was present or absent. Imaging techniques such as selective gonadal venography, and more recently ultrasound, have proved unreliable for this purpose in children. The HCG stimulation test was favoured as an alternative to laparotomy for the investigation of bilateral impalpable testes. This investigation, involving a series of injections and venepunctures, was never popular with children and yielded information of less practical value than that obtained by laparoscopy. The response to HCG of a healthy unilateral intrascrotal testis invalidates the use of the HCG test to establish the presence or absence of an impalpable contralateral testis. Furthermore, there is at issue the reliability of a negative HCG response in a pre-pubertal boy. We have been unable to find any reliable data on the long-term predictive outcome of HCG tests performed in early childhood. We believe that laparoscopy, a simple day-case procedure with a very low complication rate, excludes the possible presence of intra-abdominal testicular tissue with a higher degree of certainty than the HCG stimulation test. Whilst this test may still have a role in the investigation of some boys with cryptorchidism, it is laparoscopy which is more likely to yield information of practical relevance to surgical management—particularly in cases of unilateral impalpable testis.

Although this study does include 1 boy who underwent a 1-stage Fowler Stephens procedure, despite the presence of a healthy contralateral testis in the scrotum, we have been swayed increasingly by the argument for orchiectomy rather than orchiopexy for the unilateral intra-abdominal testis.

Studies such as that of Ford *et al.* (1985), which documented a 25% incidence of carcinoma *in situ* in post-pubertal intra-abdominal testis, support the view that there is an appreciable malignant potential in these gonads. Bianchi (1984) argued in support of his policy of performing microvascular transfer in cases of unilateral intra-abdominal testis. We do not share this view and would generally advise orchiectomy if the contralateral testis is normal. In the case of bilateral intra-abdominal testes, or when 1 testis has atrophied following unsuccessful orchiopexy, it is a very radical move to render the individual anorchid to abolish the risk of malignancy. In the absence of any functioning testicular tissue the exogenous management of puberty may be difficult. Infertility is a certainty and lifelong testosterone replacement a likely necessity. In these rare and difficult situations we believe that surgery may be justifiable to bring 1 testis (or possibly both testes) to the scrotum as a source of endogenous testosterone which can then be assessed clinically sonographically and possibly by biopsy for evidence of malignancy.

The optimum age for performing this type of surgery is arguable. In this study the mean age at operation (8.2 years) and the number of post-pubertal boys simply reflect the fact that most were referred late. Although the benefits of early orchiopexy are, as yet, largely theoretical, there is no virtue in deferring surgery beyond the age when it become technically feasible. At present the spermatic vessels are likely to be amenable to microvascular procedures at around the age of 5 years. The Fowler Stephens procedure can be performed at an earlier age. In future, fewer post-pubertal boys are likely to undergo this form of surgery, but in this situation biopsy to exclude tumour or carcinoma *in situ* is mandatory. Following either a Fowler Stephens or a microvascular procedure for intra-abdominal testis the patients must be instructed on testicular self-examination when they reach puberty and arrangements must be made for lifelong follow-up.

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Case Reports

Acute Scrotal Pain in Two Brothers

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Torsion of the testis and of the testicular appendage is not uncommon and in many cases a clear distinction cannot be made. In these cases urgent exploration of the testis is required.

Case Report

A 14-year-old boy was admitted as an emergency with a history of sudden onset of pain in his right testis. The pain radiated into his groin and was severe enough to give him difficulty in walking. His father gave a history of the boy lifting a heavy load of gravel the previous day and he felt this had caused a strain. On examination the testis was tender but normal in size; microscopy of urine was normal. He was thought to have testicular torsion and underwent an emergency exploration of testis. The testis was found to be normal and a window orchiopexy was performed.

The following day his 9-year-old brother was admitted as an emergency with a 24-h history of increasingly severe left scrotal pain which prevented him from walking. He had no urinary symptoms. The father again attributed the pain to his lifting gravel on the same occasion as his brother. On examination the left testis was tender and swollen with erythema of the left hemiscrotum; microscopy of urine was normal. At emergency exploration of the testis he was found to have a gangrenous testicular appendage twisted on its pedicle. This was excised and a window orchiopexy performed. Both boys were well at follow-up.

Comment

The appendix of the testis is a small pedunculated nodule attached to the upper pole of the testis or in a groove between it and the globus major of the epididymis and represents an intrascrotal relic of the mesonephric or paramesonephric ducts. Torsion of the testicular appendage occurs most frequently around puberty and presents as pain referred to the scrotum, groin or abdomen. On examination there is swelling and erythema of the hemiscrotum and a palpable tender blue nodule can be found in 21% of cases (McCombe and Scobie, 1988). In contrast, testicular torsion presents with

more systemic upset in the form of vomiting, lower abdominal pain and groin pain. If the blood supply to the testis is impaired, it is viable for only 6 to 8 h and immediate surgical exploration is required to confirm the diagnosis and ascertain the viability of the testis. Where the diagnosis can be made, torsion of an appendage may be managed conservatively (Holland *et al.*, 1981).

In this case it was unclear which brother developed scrotal pain first and whether the elder brother had genuine symptoms or not. In a study of children admitted to hospital with acute scrotal pain, 3% had normal or minimal findings at exploration of the testis. It also showed that 3% gave a history of vigorous exercise or exertion prior to the onset of pain (Knight and Vassy, 1984). Whenever there is doubt as to the diagnosis, however, early exploration is important.

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Renal Carbuncle Presenting as Acute Peritonitis in Pregnancy

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Case Report

A 20-year-old primigravida, new to the area and having had limited antenatal care, presented at term with irregular uterine contractions and an 18-h history of feeling unwell. Three hours before admission she suddenly developed severe left-sided abdominal pain and vomiting. She complained of urinary frequency but not of dysuria. Four weeks previously she had received flucloxacillin for 'boils' on her leg.

On examination the patient looked unwell and had a pyrexia of 38.5°C. She was acutely tender over the left flank and loin, with guarding and rebound tenderness. The remainder of the abdomen was soft. Urine analysis was strongly positive for nitrites and microscopy demonstrated numerous leucocytes and gram-negative organisms. A diagnosis of acute pyelonephritis was made. The patient was rehydrated with intravenous fluids and commenced on intravenous ampicillin.

Ninety minutes after admission the cardiococograph appeared to show evidence of fetal distress and an emergency lower segment caesarean section was performed. On opening the peritoneum a small amount of watery pale green pus was noted. A live female infant in good condition was delivered with no evidence of any intrauterine infection. After closing the uterus laparotomy was performed. Pus appeared to be tracking down the left paracolic gutter. The left kidney had an irregular outline with 2 lobules and a hole on its medial border large enough to admit a fingertip. The right kidney felt normal. No further significant abnormality could be found other than evidence of old pelvic inflammatory disease. A diagnosis of a ruptured renal abscess was made, a large corrugated drain was placed in the left paracolic gutter and the abdomen closed. Intravenous gentamicin and metronidazole were added to her antibiotic regimen.

Post-operatively the patient appeared symptomatically much improved but remained pyrexial. Drainage from the abdominal drain was light. The urine culture had grown *Escherichia coli* sensitive to her current antibiotics. Abdominal ultrasonography demonstrated 2 left-sided renal carbuncles. The larger (on the lateral margin) was 48 mm in diameter, the other 30 mm at the inferior pole. No other intra-abdominal fluid collection was detected. Intravenous urography showed a normal right kidney and expansion of the lower pole of an otherwise normal left kidney. The peritoneal swab and fluid both yielded a heavy growth of *Staphylococcus aureus* on culture,

resistant to penicillin but sensitive to cloxacillin. As a consequence her antibiotic regimen was altered to cloxacillin and Fucidin. Closer questioning revealed no history of drug abuse. HIV antibody testing was negative and there was no evidence of tuberculosis.

For the next 48 h her pyrexia and loin tenderness continued. Repeat ultrasound scan showed that the carbuncles had increased in size. As a consequence, 30 ml of thick pus (which yielded *Staphylococcus aureus* on culture) were drained percutaneously. Subsequently the patient's condition improved clinically and serial ultrasound showed the carbuncles diminishing in size, with complete resolution of the lower lesion in 3 days and the mid-zone lesion reduced to 35 mm diameter by 10 days. The antibiotics were changed to oral preparations at 6 days and continued for 4 weeks. Unfortunately, long-term follow-up has not been possible as the patient has left the area.

Comment

Renal carbuncles are a rare condition historically related to blood-borne staphylococcal infection. More recently, ascending gram-negative organisms have been implicated (Br. Med. J., 1978). Although there are 13 reported cases (including 1 in pregnancy) of intraperitoneal rupture of a pyonephrosis (Egwuatu, 1984), we believe this is the first report of a renal carbuncle rupturing into the peritoneal cavity.

Renal carbuncles can be successfully treated with antibiotics if diagnosed at an early stage (Konetschnik *et al.*, 1982). In this case percutaneous drainage was undertaken as there had been no clinical improvement within 48 h. Careful observation and serial ultrasound are advisable during the management if open surgical drainage is not employed.

Acknowledgements

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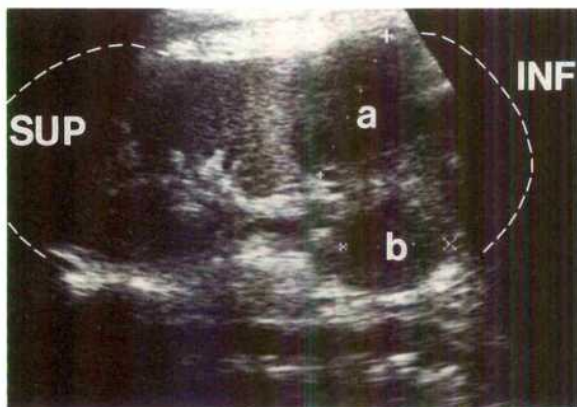


Figure Renal ultrasonogram showing carbuncles (a and b).

Tuberculous Cerebral Abscess 8 Years after Renal Transplantation

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Most infections in renal transplant recipients are caused by common pathogens. However, the incidence of tuberculosis is more common in these immunosuppressed patients than in the general population. We report a patient who developed a tuberculous cerebral abscess 8 years after receiving a kidney from a living donor.

Case Report

An 18-year-old male on haemodialysis for 2 years because of chronic renal failure received the left kidney of his mother in May 1980. The renal graft had functioned normally and the patient had enjoyed a normal life for more than 8 years.

In March 1988 he developed a high fever and a basal congestive process was seen in the left lung.

A 5-day course of 180 mg gentamicin and 100 mg Vibramycin daily cleared the pulmonary congestion. One month later he was readmitted with high fever, jacksonian-type convulsions and left brachial paresis.

Electroencephalography showed diffuse right temporo-parieto-central modification. In this area a cerebral scintiscan and CT scan revealed a pseudocystic, thick-walled, space-occupying lesion, with slight displacement of the posterior horn of the right lateral ventricle highly suggestive of cerebral abscess (Figs 1 and 2).

An encapsulated 5 × 5 cm abscess was enucleated.

Under intensive treatment with isoniazid 10 mg/kg/day, ethambutol 25 mg/kg/day and pyrazinamide 1.5 g/day the patient had an uneventful post-operative course and was discharge symptom-free after 2 weeks.

Numerous acid-fast bacilli (50–60/hpf) were seen on Ziehl-Neelsen slides and pus culture on Loewenstein medium grew the same mycobacteria.

During this time the patient's renal function remained unchanged (creatinine clearance 116/ml) and he resumed his normal way of life on azathioprine 75 mg/day, prednisone 25 mg every other day plus the above antituberculous therapy. When seen in October 1989 he was doing well.

This patient is of interest because of the long interval between successful renal transplantation and the development of a tuberculous cerebral abscess. Most tuberculous manifestations in immunosuppressed transplant patients are either pulmonary or osseous and cerebral localisation seems extremely rare.



Fig. 1 Cerebral scintiscan (16 October 1988) showing parieto-occipital area of increased density.



Fig. 2 CT scan showing right posterior parietal abscess.

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Actinomycotic Vesico-uterine Fistula from a Wishbone Pessary Contraceptive Device

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Case Report

A 77-year-old lady (gravida 4, para 4) was admitted with sudden onset of heavy vaginal bleeding for 24 h. She gave a history of being continually incontinent of urine for 3 years for which she wore pads. A wishbone-type pessary had been inserted in 1945 and this had never been removed.

The wishbone was removed under anaesthesia with difficulty, since the vagina was found to be stenosed. A necrotic cavity above the vaginal stricture then discharged spontaneously, releasing about 50 ml of pus. Leakage from the uterus of a clear fluid resembling urine was noted. Cystoscopy confirmed a large fistula at the bladder base close to the right ureteric orifice. Bacterial culture of the pyometra grew *bacteroides* and *actinomyces*. She was catheterised and treated with a course of ampicillin and metronidazole.

Five weeks later a cystogram (Fig. 1) revealed leakage from the left side of the bladder into the vagina. A formal closure of the fistula was planned.



Fig. 1 Cystogram confirming leakage into the vagina via the unresolved fistula.

On abdominal approach the bladder was found to be adherent to the cervix and lower uterus, requiring a difficult dissection to locate the fistula, which was closed with the aid of omentum. Post-operatively her symptoms of incontinence settled and a cystogram confirmed that the fistula was closed (Fig. 2).



Fig. 2 Post-operative cystogram showing some irregularity posteriorly at the site of fistula closure. No leakage demonstrated.

Comment

Only 1 case has previously been reported of a vesico-uterine fistula due to a long-standing intra-uterine contraceptive device (IUCD) which presented 14 years after a Maslin Spring IUCD had been inserted (Schwartzwald *et al.*, 1986). Actinomycosis had been identified only recently and has been reported in patients with IUCDs (Hager and Majmudar, 1979). Culture reveals the typical fastidious anaerobic gram-positive, non-sporing organism with branching filaments. As it cannot invade intact mucous membranes and requires previous tissue injury or the presence of a foreign body to establish infection, the IUCD is an ideal predisposing factor to the development of pelvic actinomycosis. The complication of a vesico-uterine fistula due to a wishbone pessary has not been previously reported and the role played by actinomycosis remains speculative. Obviously the presence of such a device for 43 years is exceptional.

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Multifocal Ureteric Amyloidosis

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Case Report

A 54-year-old welder was referred with a 2-month history of pain in his right loin radiating to the groin but no haematuria or other urinary symptoms. Blood and urine investigations were normal, including urine cytology. Intravenous urography revealed 2 strictures in the right ureter in its middle and lower thirds with mild hydronephrosis above and a normal left system (Fig. 1).

Cystoscopy, ureteroscopy and retrograde pyelography showed papillary changes distal to a stricture 3 cm from the right ureteric orifice, beyond which no contrast passed. Although the biopsies taken were inconclusive, a presumed diagnosis of transitional cell carcinoma was made.

At operation 2 friable tumours were found, 1 measuring 2 cm in the lower ureter and the other measuring 7.5 cm in the middle third. A right nephroureterectomy was therefore performed, from which he made a good recovery.

Histology revealed eosinophilic material within the ureteric wall, which showed positive staining with congo red and apple green birefringence, characteristic of amyloidosis (Fig. 2). The kidney was normal and further staining showed AL type amyloid, found in primary amyloidosis. Bence Jones proteinuria and monoclonal gammopathy were not found, excluding myeloma, and multifocal primary amyloidosis of the right ureter was diagnosed.

Comment

A total of 29 cases of primary ureteric amyloidosis have been reported since Lehman described it in 1937. It is commoner in women (18 of 30) and on



Fig. 1 IVU showing 2 strictures in the middle and lower third of the right ureter.

the left (17 left, 9 right, 4 bilateral). Farrands *et al.* (1983) observed it more frequently in the lower third and only rarely in the middle third (9 lower; 3 upper; 1 middle). In none was the diagnosis made pre-operatively and although ureteroscopic biopsy is now advocated (Gulmi *et al.*, 1988), it did not help in our case.



Fig. 2 Low power view of ureteric wall showing deposition of amyloid.

Of 28 patients operated on, 18 had a nephroureterectomy, 4 a local resection and reimplantation, 3 a resection and end-to-end anastomosis, 2 a resection and renal autotransplantation and 1 a resection and substitution with ileum.

The operative appearance in our case was indistinguishable from that of transitional cell carcinoma and explains the number of radical operations performed. Recent reports (Primrose *et al.*, 1985; Gulmi *et al.*, 1988) suggest that frozen section at operation would allow a more conservative approach to be taken if appropriate and we would concur with this. The 2 separate tumours make our case unusual and, if a conservative approach had been taken, autotransplantation or reconstruction would have been required.

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Venous Bypass and Filtration during Nephrectomy for Renal Carcinoma with Tumour Thrombus in the Retrohepatic Cava

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Excision of renal carcinoma with tumour thrombosis involving the retrohepatic vena cava remains a technical challenge. We describe the use of a venous bypass and filter which carried blood from the suprahepatic vena cava to the right atrium via an external filter. This device carried venous return from the retrohepatic cava, including that from the liver, maintained a satisfactory cardiac output and enabled the controlled removal of tumour thrombus whilst diminishing the risk of tumour embolus.

Some 5% of patients with renal carcinoma are found to have extension of the tumour into the vena cava, but have no evidence of distant metastases: they are thus potential candidates for complete local excision of the tumour (Skinner *et al.*, 1972; Giuliani *et al.*, 1990). Thrombosis limited to the infrahepatic vena cava can usually be dealt with by additional local technical manoeuvres during radical nephrectomy, including mobilisation and isolation of the infrahepatic vena cava by ligation of the small hepatic veins which pass directly from the caudate process into the anterior surface of the cava, followed by temporary occlusion of the cava above the thrombus, of the contralateral renal vein and of the infrarenal cava (Marshall *et al.*, 1988). However, in one-fifth to one-quarter of patients with thrombus, it extends beyond the lower border of the liver and its removal requires special techniques. Manoeuvres such as temporary occlusion of the intra-pericardial or suprahepatic cava may be used, but in many patients severe decreases in cardiac output are the result (Cummings *et al.*, 1979). If the thrombus extends to the right atrium, transfer of the patients to complete hypothermic

cardiopulmonary bypass is required, but this procedure holds its own risks and may be unnecessary for patients with tumour thrombus extending above the lower border of the liver but not reaching the pericardium. One technique of venous bypass in the treatment of such patients was described by Attwood *et al.* (1988). This involved the insertion of cannulae in the femoral vein and right atrium and the use of a pump and filter to transfer the venous return from the femoral vein to the right atrium after occlusion of the intra-pericardial inferior vena cava. We describe an alternative technique which does not necessitate exposure and cannulation of the femoral vein with the subsequent risk of thrombosis, can avoid the use of a pump and has the advantage of providing filtration of the venous return from the retrohepatic cava.

Case Report

A previously fit 75-year-old man presented with a 6-month history of haematuria and an abdominal swelling. Physical examination confirmed a large, right-sided renal mass apparently in continuity with the liver. There was no lymphadenopathy, engorgement of abdominal wall veins or impairment of venous return from the lower limbs. His preoperative creatinine was 138 $\mu\text{mol/l}$. Initial ultrasound scanning demonstrated a large renal mass with no apparent involvement of the renal veins or cava and a chest X-ray demonstrated no metastases. CT confirmed the presence of a large, partly solid mass (Fig. 1) with no apparent involvement of the vena cava (Fig. 2), no lymphadenopathy and no pulmonary metas-

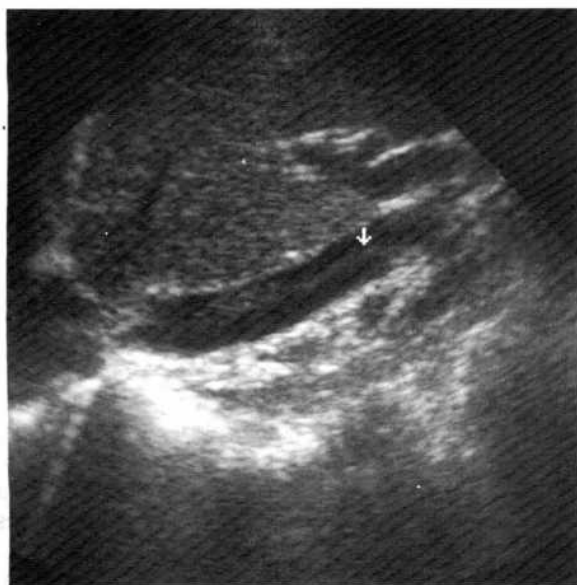


Fig. 1 CT demonstrating large right-sided renal carcinoma.



Fig. 2 CT demonstrating upper pole of right kidney with normal vena cava.

tases. However, invasion of the body wall or liver by tumour could not be excluded and a further ultrasound scan was advised. This study did not help with this problem, but did show a large tumour thrombus extending from the renal vein to the retrohepatic cava, but not reaching the right atrium (Fig. 3). A joint approach with the cardiothoracic surgeons was planned with a view to performing venous bypass of the retrohepatic cava.

The radial artery was cannulated and a central venous line was inserted in the right jugular vein for continuous monitoring of the arterial and central venous pressure. The kidney was approached via a transverse incision extending from the mid-axillary line to the mid-point of the contralateral rectus sheath. The tumour was large with many filmy, vascular adhesions attached to the right mesocolon and liver. These, together with large collateral vessels passing to the abdominal wall, were carefully ligated and divided. The tumour was not directly invading the vena cava, liver or bowel and there were no signs of metastatic disease.

A median sternotomy was then performed, the pericardium was opened using an inverted T incision, stay



Fig. 3 Ultrasound scan demonstrating a tumour thrombus (arrowed) extending into retrohepatic cava, almost to level of diaphragm.

stitches were placed and the heart was exposed; sharp dissection of the pericardial reflection of the inferior vena cava (IVC) was performed and a tape was placed around it. Two purse-string sutures of 2-0 Ethibond were placed in the right atrium, one in the appendage, the other just above the IVC. Two pre-clamped, soft silicone venous cannulae 7 mm in diameter filled with normal saline were inserted through the purse-string sutures and secured. One entered the suprahepatic cava and was to carry the venous return from the lower part of the body when the sling around the intra-pericardial cava was tightened and when the clamp was loosened later in the operation. The other tube passed into the upper part of the right atrium. The 2 tubes were connected via two 40 μ blood filters (Stat Prime, Pall Biomedica Ltd) which were primed with 150 ml of normal saline and which were in parallel. One filter was not in circuit and was a reserve in case the other filter became blocked with tumour cells or debris.

The inferior vena cava and left renal vein were mobilised and the right renal artery was ligated between the aorta and cava. The right triangular and coronary ligaments were divided, allowing the liver to be swung forward and exposing the retrohepatic cava (Marshall *et al.*, 1988). The kidney was then mobilised, leaving the renal vein intact.

The patient was then fully heparinised with 2 mg/kg of heparin keeping the activated clotting time above 300 s. The sling around the IVC was tightened and the clamps were removed from the silicone tubing, allowing all of the venous return from the lower body through the filter and back into the right atrium. The venous return (~ 750 ml/min) was adequate to maintain cardiac output and the system protected the patient from a massive tumour embolus. The Rummel tourniquets were then tightened around the left renal vein, the infrarenal inferior vena cava and a soft bowel clamp was placed across the porta hepatis.

A longitudinal venotomy was fashioned in the cava above the renal vein and the thrombus was removed. Some back-bleeding remained despite the bypass, but this was controllable and was probably potentially beneficial in allowing any small fragments of thrombus to be washed out of the cava. Air was removed from the cava by venting and the venotomy was closed with 6-0 Prolene. The heparinisation was reversed with protamine, drains were placed to the pericardium and renal bed and the incisions were closed. The operating time was 4 h and blood loss was 2.2 L.

After operation, the patient developed bronchopneumonia which required physiotherapy and antibiotics and also had episodes of atrial fibrillation which were treated by digitalisation. Histology of the resected specimen demonstrated no lymph node involvement, but invasion through the capsule had occurred. The thrombus consisted of tumour. Cytological examination of the filters from the venous bypass demonstrated no malignant cells.

The patient was discharged 2 weeks after operation and was in good health when seen 2 months later, with no evidence of metastases on chest X-ray and bone scan.

Comment

The use of intraluminal intubation of the inferior vena cava has been described previously in the management of patients with trauma (Schrock, 1982; Burch *et al.*, 1988); for patients with tumour thrombus, however, such techniques carry the risk of embolus, although they should permit adequate control of bleeding. Total clamping of the IVC (Cummings *et al.*, 1979) carries the risk of producing a precipitate fall in cardiac output.

The use of an external venous bypass between the femoral vein and right atrium connected via a roller pump to facilitate the removal of a renal carcinoma with vena caval tumour thrombus has been reported previously (Attwood *et al.*, 1988; Launois *et al.*, 1989). This procedure is safe and, because of the use of the pump, the venous return is good and the pressure within the cava is low with a decreased risk of venous bleeding. On the other hand, it requires a trained perfusion technician, haemodilution to prime the pump and a reservoir to collect the blood. It can only be performed in institutions with full cardiac surgical facilities and carries the attendant risks of extracorporeal bypass, namely platelet destruction, haemolysis, high levels of per-operative anticoagulation and an additional incision to expose the femoral vein with a subsequent risk of venous thrombo-embolic disease. It also leaves that part of the vena cava above the tumour thrombus undrained with the possibility that small tumour emboli might occur after the main mass of thrombus had been removed when the sling around the intra-pericardial cava had been removed.

The potential advantages of the technique described here are that it can be performed in institutions without facilities for full extracorporeal cardiac bypass and it provides satisfactory control of bleeding with an adequate venous return. It also avoids the risks of extracorporeal bypass and the need for exposure and cannulation of the femoral vein. In addition, the use of the filter ensures that fragments of tumour thrombus which might be dislodged should be arrested before return to the right atrium.

The question of survival of patients with tumour thrombus in the vena cava and renal vein has been addressed previously (Skinner *et al.*, 1972). It is important to distinguish direct infiltration of the cava (which is associated with a poor survival) from tumour thrombus, for it is questionable whether patients with direct infiltration of the cava should undergo radical surgery. If invasion of perirenal fat

or lymph nodes is present or distant metastases are found, then survival is poor regardless of venous thrombosis. On the other hand, if these features are absent, then survival of patients with vena caval thrombosis after radical surgery is about 50% at 5 years (Skinner *et al.*, 1972), although others have reported less optimistic results (Marshall *et al.*, 1988; Giuliani *et al.*, 1990). The extent of vena caval involvement is also important because patients with extensive tumour thrombi reaching above the hepatic veins often have associated poor prognostic factors (Marshall *et al.*, 1988; Giuliani *et al.*, 1990). A recent report by Skinner (1990) has confirmed this view; those with extension into the infrahepatic and retrohepatic cava having 5-year survivals of 42 and 20% respectively—none of the patients with more extensive disease survived 5 years. In the absence of metastases or direct tumour infiltration, patients with intraluminal extension into the infrahepatic and retrohepatic cava should be considered for radical surgery. We believe that the technique described here may be useful in such patients and offers the advantage of providing vascular control and diminishing the risk of tumour embolisation during surgery.

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Incidental Renal Carcinoma Discovered during Ultrasound Localisation of Renal Calculi for Extracorporeal Piezoelectric Lithotripsy

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Extracorporeal shock wave lithotripsy is now widely used for the treatment of urinary calculi. Some lithotriptors, such as the Wolf 2300 Piezolith in this centre, use ultrasound imaging to localise and focus on to the stone prior to treatment. We have discovered 2 unsuspected renal carcinomas during this process, both of which were not revealed by the intravenous urogram sent with the referral. Prompt surgical intervention showed that both tumours were confined to the pathological specimen.

Case Reports

Case 1. A 50-year-old man attended for extracorporeal lithotripsy. Four months previously he had presented to a referring hospital with mild left loin pain, when an intravenous urogram revealed a 6-mm calculus in a left lower calix. There was no other abnormality. While locating the calculus on the lithotripter the urologist noted a solid mass in the mid part of the kidney. This was confirmed by diagnostic ultrasound imaging. Subsequent renal angiography demonstrated a tumour circulation and a radical nephrectomy was performed. Histology demonstrated a 5 × 4 × 4 cm renal carcinoma confined by the renal capsule, Robson Stage 1.

Case 2. A 66-year-old woman attended for extracorporeal lithotripsy. She had presented to her referring hospital 7 months previously with a history of recurrent urinary tract infection and an episode of haematuria. A 19-mm calculus lying in a right lower calix was the only abnormality demonstrated by intravenous urography. Cystoscopy and bladder biopsy had shown inflammation. A mass was discovered in the mid part of the kidney by the urologist carrying out localisation of the calculus. Digital subtraction angiography of the renal vessels confirmed the presence of a tumour circulation and the patient underwent a radical nephrectomy. Histology demonstrated a renal carcinoma of maximum diameter 5.5 cm and with a small area of invasion into the soft tissues of the renal pelvis, Robson Stage 2.

Comment

In this centre the intravenous urogram of each new patient is scrutinised by a consultant radiologist and 2 consultant urologists prior to acceptance for extracorporeal lithotripsy. It seems likely that both patients would have undergone lithotripsy if they had been treated on a machine which uses fluoroscopy for localisation of calculi. Discovery of the tumours would have been delayed. The effect of shock wave treatment in proximity to tumours is uncertain. Direct focusing of high energy shock waves suppressed the growth of an experimental prostatic carcinoma *in vitro* and in an animal model (Russo *et al.*, 1986). However, the application of shock waves in proximity to tumours *in vivo* may be harmful by production of tumour microemboli.

In a large series of autopsies, renal carcinomas which had been unrecognised throughout life were found in 1.4% of cases (Hellsten *et al.*, 1981). In clinical series, the proportion of renal carcinomas discovered incidentally appears to be increasing and is currently around 15%, with 78% of these tumours being confined to the kidney at the time of presentation (Ritchie and deKernion, 1988). We have discovered unsuspected renal carcinoma in 2 of 1100 patients presenting for lithotripsy. The presence of the calculi may have deterred further investigation leading to the discovery of these tumours; 42% of our patients were aged below 50 years and the disease is very rare in this age group. The findings raise the question of whether all patients over 50 years of age ought to undergo ultrasound scanning prior to extracorporeal lithotripsy, especially until our knowledge of the effects of shock waves on tumours is greater. Discovery prior to lithotripsy represents a previously unreported scenario for the detection of renal carcinoma.

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Oral Trazodone in the Treatment of Total Secondary Impotence in a Diabetic Patient

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The antidepressant trazodone differs in both pharmacological properties and structure from the tricyclic antidepressants and offers some advantages over them in terms of side effects and toxicity. However, there are reports of priapism as a side effect associated with the oral use of trazodone and alpha-adrenoceptor blocking activity was suggested as the mechanism. It is known that the intracavernous injection of alpha-adrenoceptor blocking agents produces erection (Brindley, 1983). We report the effect of oral trazodone in the treatment of impotence.

Case Report

S.A.K. was a 45-year-old man with a steady marital partner and 3 children aged 22, 21 and 18 years. He had had an active sexual life until 5 years previously, when his ability for penile erection deteriorated gradually to total impotence. He was mildly hypertensive (160/100) but not on oral medication for this. He had been diabetic for 5 years and was taking an oral hypoglycaemic agent (Daonil). His follicle-stimulating hormone and testosterone levels were normal and prolactin was low at 32 mIU/L. Neurological tests (using median sensory, median motor and sural sensory nerves) indicated abnormal responses and he was diagnosed as having mild polyneuropathy due to diabetes. His bulbocavernous reflex was also absent.

He responded well to the intracavernous injections of prostaglandin E₁ (PGE₁) for his impotence (Virag and Adaikan, 1987). The optimal effective dose of PGE₁ titrated for him was 40 µg. Based on this dosage, the time taken for erection and the pattern of erection, together with neurological tests and medical history, he was diagnosed as having moderate to severe arteriogenic/neurogenic impotence (Adaikan *et al.*, unpublished data). However, the effectiveness of PGE₁ indicated, at least in part, normal vascular/cavernosal integrity within the penis. He had been on a self-injection programme using PGE₁ for 15 months but in view of his unease about long-term dependence on intracavernous injections and his wish for alternative medication, we embarked on a trial of oral trazodone. A 30-day course of vitamin E (100 mg/day) had proved ineffective.

Table Oral Trazodone in the Treatment of Impotence

Period of Treatment	Dosage	Erection/coitus	Side effects
4 weeks	150 mg 2 h before attempting intercourse	Soft erection for 10 min	—
2 weeks	50 mg <i>tds</i>	Penetrable erection and 1 successful coitus	Drowsiness
4 weeks	50 mg <i>bd</i> for 1 week followed by 3 doses (150 mg) 1 h before attempting coitus	Penetrable erection and successful coitus at every attempt	Drowsiness and cold extremities. The non-erect penis was elongated by 2½ cm during treatment

In the first protocol, involving 4 attempts at coitus at weekly intervals, trazodone 150 mg (three 50 mg capsules) was taken 1 to 2 h before each attempt. The patient achieved a brief soft erection lasting for about 10 min but this was insufficient for penetration. Over the following 2 weeks he was given 50 mg trazodone *tds*; he achieved a penetrable erection and 1 successful coitus. In the subsequent 4-week trial he took trazodone 50 mg *bd* in addition to trazodone 150 mg (three 50 mg capsules) 1 h before attempting coitus (once a week). He achieved a penetrable erection and successful coitus at each attempt and the penis returned to a non-erect state after ejaculation. The only side effect was drowsiness during the day and on one occasion he reported cold extremities. During this trial, he also observed elongation of the non-erect penis by at least 2½ cm (Table). There were no obvious signs of mood elevation.

Comment

Trazodone has shown marked alpha-1 adrenoceptor antagonism to noradrenaline-induced contraction of the human corpus cavernosum *in vitro* (Adaikan and Ratnam, 1988). Since inhibition of adrenergic activity is necessary for the physiological development of erection (Adaikan, 1979) and the intracavernous injection of alpha-adrenoceptor blocking agents results in erection, trazodone-induced erection in impotent patients is likely to be a manifestation of alpha-adrenoceptor antagonism. Thus, trazodone or other suitable alpha-adrenoceptor blocking agents titrated to an effective dosage may be an ideal approach to oral treatment for impotence (Adaikan and Ratnam, 1988).

Trazodone-induced priapism is likely to occur within the first 28 days of treatment and is usually associated with doses of 150 mg/day or less,

irrespective of age, when given as an antidepressant (Warner *et al.*, 1987). When patients are already suffering from impotence, and especially if the dosage is titrated to achieve minimal erection sufficient for coitus, priapism-like conditions are unlikely to occur.

We believe that this successful treatment of impotence with oral trazodone is not a placebo effect because our patient had a 5-year history of total secondary impotence and was also unable to achieve spontaneous erections in between the weekly PGE₁ treatments. Further studies are necessary to establish the efficacy of this treatment.

Acknowledgements

We thank Professor B. Silvestrini, Instituto di Ricerca F. Angelini, for samples of trazodone and Ms Safurah for secretarial assistance.

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Requests for reprints to: P. G. Adaikan, Department of Obstetrics and Gynaecology, National University Hospital, Lower Kent Ridge Road, Singapore 0511.

Points of Technique

Relationship between Segmental Arteries and Pelviureteric Junction

F. J. B. SAMPAIO, *Department of Anatomy, State University, Rio de Janeiro, Brazil*

Since the first description of percutaneous endopyelotomy by Wickham and Kellett (1983) and its subsequent popularisation (Badlani *et al.*, 1986), this procedure has become an effective alternative to standard open pyeloplasty in the management of pelviureteric junction (PUJ) obstruction. More recently, a method of performing endopyelotomy through the ureteroscope has been reported (Clayman and Picus, 1988).

Regardless of the route chosen, to achieve success one must incise the entire thickness of the PUJ stenotic wall as far as periureteric fat. This deep

incision carries the risk of injuring an artery, but the risk can be greatly reduced if the vascular relationship is borne in mind.

In order to study the relationship between segmental arteries and the PUJ, we analysed 82 3-dimensional polyester resin corrosion endocasts of the renal collecting system together with the renal vasculature. In 52% of cases there was a close relationship between the inferior segmental artery and the anterior aspect of the PUJ (Fig. 1A) when this vessel passed in front of this region to enter the inferior pole. This is a consistent anatomical relationship of a normal segmental artery. One must therefore incise the wall of the PUJ posterolaterally to avoid an arterial lesion. In 1 case there was 1 artery anterior and another artery posterior to the PUJ; thus the area to be incised, including the posterolateral wall, should be examined for arterial pulsations. In the remaining 46% of cases the PUJ was not related to arterial vessels (Fig. 1B). An understanding of the relationship between the PUJ and the arteries is essential to the safe performance of endopyelotomy.

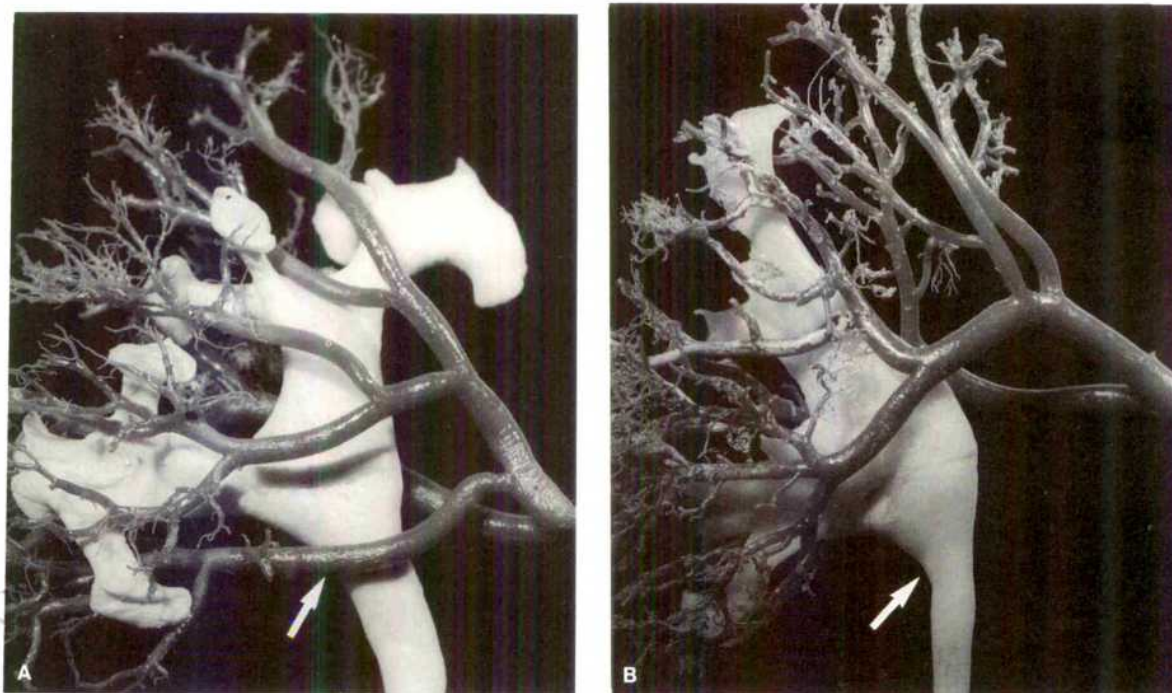


Fig. 1 (A) Anterior view of endocast from right kidney showing close relationship between inferior segmental artery and anterior aspect of the PUJ (arrow). (B) Anterior view of endocast from right kidney showing PUJ area with no relationship to arterial vessels (arrow).

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Requests for reprints to: F. J. B. Sampaio, Department of Anatomy—U.E.R.J., Caixa Postal no. 46503, 20562 Rio de Janeiro, RJ Brazil.

An Aid to Rigid Ureteroscopy—Stone Basket

P. VIJAYAN, *Department of Urology, Hamad Medical Corporation, Doha, Qatar*

In centres where extracorporeal shock wave lithotripsy is not available, ureteroscopy has established itself as the method of choice for the removal of calculi from the ureter.

Some authors advocate threading the ureteroscope over a guidewire (Ellendt and Martinez-Pineiro, 1982) and others suggest passing a ureteric catheter through the instrument channel to provide a continuous irrigation system and to avoid overdistension of the ureter (Raju, 1988). In the undilated ureter the beginner and even the experienced surgeon can experience difficulty in passing the instrument and great care is required to avoid complications. Successful advancement should follow if the ureter can be kept "opened up" until the stone is reached.

Once the ureteroscope has entered the ureter above the intramural level alongside the guidewire, a stone basket with a filiform tip is passed through the instrument channel and the basket is opened. Further advancement of the ureteroscope becomes easy and the upper reaches of the ureter are quickly accessible. When the stone is visualised it can be engaged in the wire basket under vision or the basket can be replaced with an ultrasonic burr. The filiform tip of the basket seems to act as a second guidewire and the opened basket keeps the ureteric walls away from the tip of the advancing ureteroscope (Fig.).

This technique has been used successfully on 20 patients and there have been no complications.

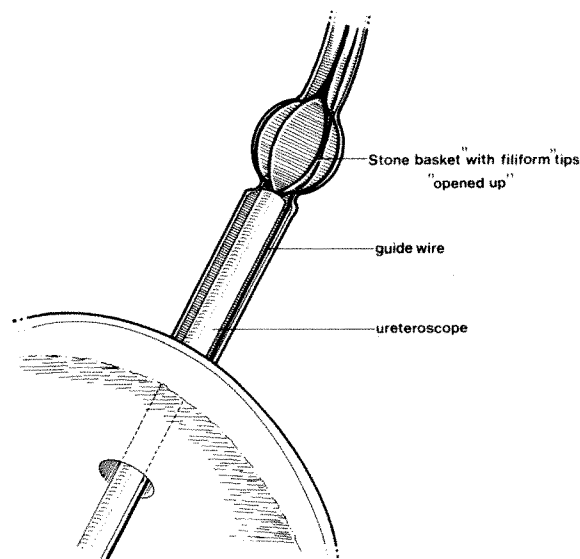


Fig.

References

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Requests for reprints to: P. Vijayan, Consultant Urologist, P.O. Box 3050, Hamad Medical Corporation, Doha, Qatar.

Stenting the Extravesical Ureteroneocystostomy in Kidney Transplantation

K. GERMAN and O. N. FERNANDO, *Department of Nephrology and Transplantation, Royal Free Hospital, London*

Extravesical ureteroneocystostomy is becoming a more popular method for urinary tract reconstruction in kidney transplantation (Barry, 1983). The procedure involves a small cystotomy and only limited exposure of the bladder. A technique for stenting the anastomosis has been developed which allows accurate placement of the stent without the need for a large cystotomy.

Technique

A Foley catheter is inserted into the bladder under aseptic conditions and connected to a saline bag

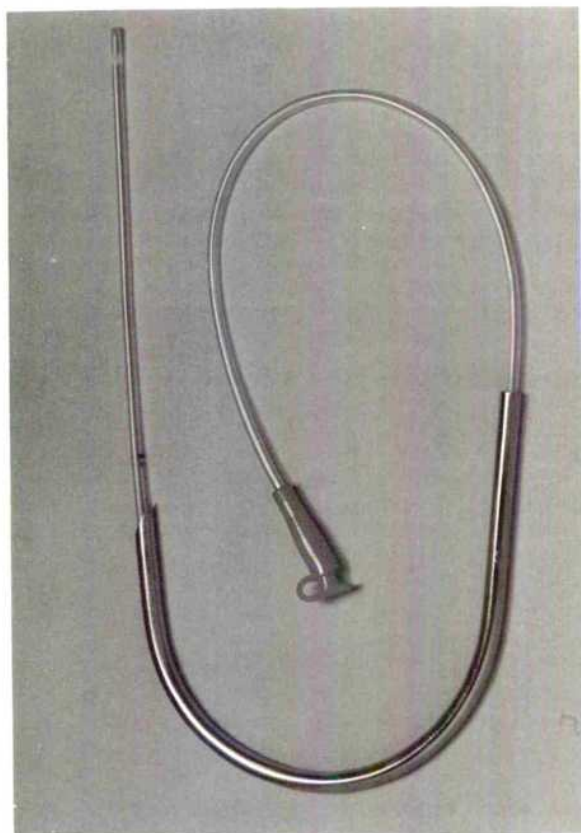


Fig. 1

and giving set. After the vascular anastomoses have been completed, the bladder is filled with 200 ml of saline. The detrusor muscle is then divided to expose the bladder mucosa. The stent introducer is a C-shaped stainless steel tube, with one end sharpened. It will allow the passage of a stent up to 10 F (Fig. 1).

Using the stent introducer, an 8 to 10 F infant feeding tube is tunnelled through the anterior abdominal wall. The introducer and stent are then inserted into the bladder away from the site of previous dissection and manipulated to emerge at the site of the proposed ureteroneocystostomy (Fig. 2).

The introducer is then removed and the stent is passed up the ureter to the renal pelvis and is secured to the distal end of the transplant ureter by means of a 4/0 catgut suture. The ureteric anastomosis is completed and detrusor muscle is sutured over the ureter, thus completing the extravesical submucosal tunnel. The Foley catheter is retained for 4 days and the stent is removed on the tenth post-operative day.

Comment

The extravesical technique offers several advantages over the internal ureteroneocystostomy: (a) less ureteric length is required, (b) only minimal bladder dissection is necessary, (c) there is no need for a separate cystotomy and (d) the extravesical technique is quicker to perform. The technique has been described by several authors (Konnak *et al.*,

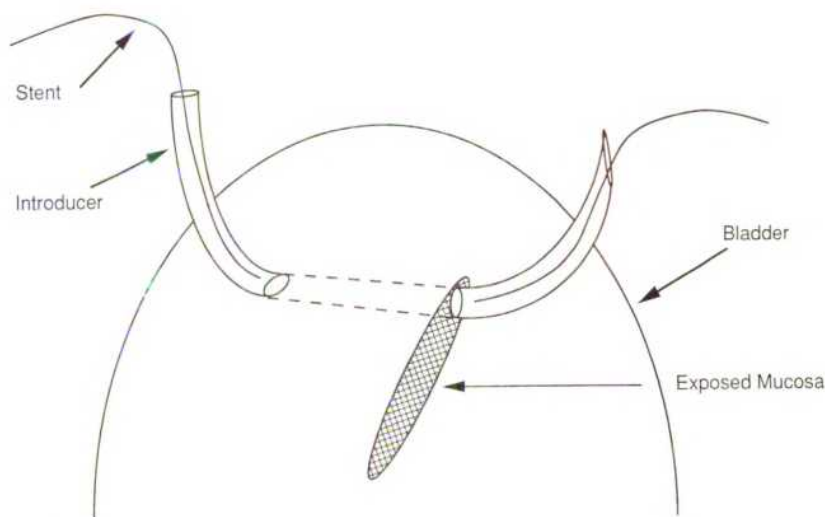


Fig. 2

1975; McDonald *et al.*, 1979; Barry, 1983) and each group has described their particular modification.

The stent enables free drainage of the transplant kidney whilst also splinting the ureteric anastomosis, thereby reducing the risk of a urinary fistula. Internal draining double J stents surgitek have been used but these require a return to the operating theatre for removal under either local or general anaesthesia. The infant feeding tube, however, may simply be pulled out at the bedside on the tenth post-operative day.

Another advantage of the external draining stent is that it provides a good estimate of the urinary output from the transplant kidney, since urine will drain down the stent rather than into the bladder (at least until the anastomotic oedema resolves). This is especially helpful in patients with polyuric renal failure, where the native kidneys produce large volumes of urine.

The introducer provides a simple and accurate method for placement of a ureteric stent in the

situation of extravesical ureteroneocystostomy. We have used this technique successfully in 20 renal transplants, so far, without any specific complications.

Acknowledgement

We thank Mr R. Humber, Dialysis Unit Workshop, for his help with the design and making of the stent introducer.

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Requests for reprints to: K. German, Department of Urology, South Cleveland Hospital, Marton Road, Middlesbrough TS4 3BW.

Correspondence

Dear Sir,

re Comparison of primary orchiectomy and polyoestradiol phosphate in the treatment of advanced prostatic cancer. R. Haapiainen *et al.* *Br. J. Urol.*, 66, 94–97, 1990.

The authors state that theirs was the first randomised trial of orchiectomy compared with a dose of a parenteral oestrogen preparation (polyoestradiol phosphate (PEP) 160 mg/month) known to give incomplete suppression of blood androgen levels. In fact we published results of an identical trial a year ago (M. C. Bishop *et al.* *Br. J. Urol.*, 64, 290–296, 1989). We would dispute that PEP 160 mg/month is invariably inadequate in the treatment of advanced prostatic cancer. We would agree that this dose leads overall to earlier progression than orchiectomy and the mean plasma testosterone levels will be well above the castrate range. However, approximately 40% of our patients on PEP 160 mg/month did achieve a sustained clinical and biochemical response comparable with that of orchiectomised patients. Their mean plasma testosterone levels were below 4 nmol/l, *i.e.* well in excess of the upper limit of the castrate range (2 nmol/l). Of the remaining patients treated with PEP, 55% achieved a secondary response to orchiectomy. Their mean plasma testosterone levels were greater than 5 nmol/l. The remainder had no secondary response to orchiectomy and had well suppressed plasma testosterone levels. They represent approximately 27% of the initial group and can be regarded as primarily hormone unresponsive. We concluded that a threshold level of testosterone suppression had been demonstrated which provided adequate hormonal control and with a mean testosterone level of 4 to 5 nmol/l.

We feel that for a significant proportion of patients, oestrogen dosage can be safely reduced without jeopardising control, allowing dose-dependent side effects to be minimised.

Yours faithfully,

M. C. Bishop
Department of Urology, City Hospital, Nottingham.

Reply by R. Haapiainen et al. We appreciate very much Mr Bishop's comments. We are encouraged

that there are other urologists interested in parenteral oestrogen treatment of prostate cancer. Unfortunately, his article on polyoestradiol phosphate (PEP) was published after we submitted our own data.

Because of the androgen dependence of most prostate cancers and the impossibility of predicting which patients will respond to hormonal manipulation, the main goal of endocrinological treatment is elimination of all androgens. As Mr Bishop showed, the majority of patients treated with 160 mg PEP do not achieve castrate levels of plasma testosterone and many of these patients respond to secondary orchiectomy, *i.e.* the oestrogen dosage was inadequate. On the other hand, based on the parenteral administration, the risk of cardiovascular complications is very low even when much higher doses are used (Henriksson *et al.* *The Prostate*, 13, 257–261, 1988). It even seems possible that in the long run PEP therapy decreases cardiovascular mortality in prostate cancer patients (Aro. *The Prostate*, 1991. In press).

In our opinion, therefore, there is no reason to reduce the PEP dosage and monitor the plasma testosterone, which is expensive. Rather the opposite: increasing the dosage seems to be safe and also guarantees a castration effect.

Dear Sir,

re Bacteriological state of the urine in symptom-free adult males. I. D. Sugarman *et al.* *Br. J. Urol.*, 66, 148–151, 1990.

In this paper the authors conclude that the finding of pyuria in adult male mid-stream urines is uncommon and should prompt the clinician and bacteriologist to seek fastidious organisms such as *Gardnerella vaginalis* as the cause if conventional culture is sterile. They then suggest that a chlamydial infection is a possibility in men with pyuria in whom both aerobic and fastidious organism culture is negative, and this is supported by recent evidence from Matthews *et al.* (*Lancet*, 336, 385, 1990), who showed that up to 10% of cases of sterile pyuria may be due to *Chlamydia trachomatis* infection. *C. trachomatis* is a common sexually transmitted pathogen (Center for Disease Control. *Chlamydia trachomatis* Infections. Policy Guidelines for Prevention and Control. *MMWR Suppl.*, 34, S53–74, 1985; PHLSCDSC. *Genitourin. Med.*, 65, 117–121, 1989), accounting for 50% of cases of non-gonococcal urethritis of which 10 to 15% may be asymptotic.

matic. It is often asymptomatic in women but has the serious sequelae, if untreated, of pelvic inflammatory disease, infertility, ectopic pregnancy and vertical transmission to the neonate resulting in conjunctivitis and pneumonitis.

I acknowledge the authors' statement that chlamydial diagnostic services are not widely available in service laboratories, but the empirical treatment with doxycycline of patients in whom a chlamydial infection is assumed completely neglects the issue of contact tracing and treatment of an infected partner. In the follow-up of patients with 'persistent' pyuria a reinfection should be excluded before embarking on early morning urine cultures for *Mycobacterium tuberculosis*.

I suggest that when the finding of sterile pyuria raises the possibility of a chlamydial infection, the patient be referred to a Genitourinary Medicine clinic where appropriate diagnostic facilities should be available. A definite diagnosis may then be made, contact tracing and treatment of sexual partners performed, and opportunity made for health education and 'safer sex' promotion.

Yours faithfully,

C. Thompson
Department of Genito-urinary Medicine, Royal Infirmary, Edinburgh.

Dear Sir,

re Ruptured bladder following circumcision using the Plastibell device. L.D. Jee and A.J.W. Millar. *Br. J. Urol.*, **65**, 216-217, 1990.

The observation of ruptured bladder following circumcision is interesting. However, the concluding remark "Careful technique and post-operative supervision in circumcision" has nothing to do with it. The statement that spontaneous rupture of the bladder almost invariably occurs in the pathological organ is wrong. We recently had 2 patients with spontaneous rupture of the bladder and both had a normal bladder wall. It is noteworthy that both of these patients had bladder neck dyssynergia and were treated with bladder neck incision. It is important to know if the authors had performed uroflowmetry in this patient. I am sure that if a urodynamic study is done together with micturating cystourethrography, one is going to find problems at the bladder neck and the present case is interesting in the sense that a ruptured bladder in

such a young patient is unusual and not that it has anything to do with the Plastibell device.

Yours faithfully,

S. Khanna

Department of Urology, Ganga Ram Hospital, New Delhi 60, India

Reply by L. D. Jee. I stand by my statement that careful technique and post-operative supervision are important in patients undergoing circumcision with a Plastibell device. This device enjoys fairly widespread use in the area around our hospital and although this is the most severe complication we have encountered, several others have already been reported (Millar and Roberts. *S. Afr. Med. J.*, **72**, 438-439, 1987). Although one must acknowledge the possibility of a second pathology, in this case I have no doubt that it was the circumcision that precipitated this patient's problem. He was a perfectly well little boy until the time of his circumcision with no evidence of abnormal voiding symptoms. He went into urinary retention post-operatively and this was not acted upon for 48 h, until the child was brought to hospital in a moribund condition. He recovered following repair of his bladder and is once again voiding normally. The statement that "spontaneous" rupture has occurred in Dr Khanna's patients with bladder neck dyssynergia reinforces the contention that this problem is seen in pathological bladders as dyssynergia must surely be included in this group of conditions. Obviously urodynamic investigations were not appropriate during the acute phase and we have not considered them to be indicated post-operatively.

Thank you for allowing me to examine the letter at this stage.

Dear Sir,

re Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. J. McLoughlin *et al. Br. J. Urol.*, **66**, 303-305, 1990.

The main aim of this study was to address the important question of the selection of men for prostatectomy.

One problem was that the authors became bogged down by the definition of obstruction using urethral

resistance. They concluded that 95% of men with flow rates <12 ml/s are "obstructed". Low flow rates must of necessity be statistically associated with a high urethral resistance (UR) because UR is calculated by dividing voiding pressure by the square of the flow rate. The authors defined "obstruction" as a high UR: that low flow rates were found to be associated with this definition of "obstruction" should therefore occasion no surprise. The authors are incorrect in suggesting that it may be possible for flow rate measurements alone to distinguish men with low flow rates and high voiding pressure from those with low flow rates and low voiding pressure—who tend to do poorly after prostatectomy (Neal *et al. Br. J. Urol.*, **60**, 554–559, 1987; Neal *et al. Br. Med. J.*, **299**, 762–767, 1989).

Their second point was that "objective measures are necessary" in pre-operative assessment, and "the importance of a screening flow rate is emphasised". The sentiments are laudable, but unsupported by any data. The important question is whether men with typical symptoms of outflow obstruction and low flow rates (<12 ml/s for the sake of argument) have a significantly better outcome than those with symptoms and greater flow rate and whether flow rate measurement can be used in selecting men for operation.

Several large studies (totalling over 400 men) have shown that flow rate measurement is insufficiently precise either confidently to deny a man an operation or confidently to reassure him of an excellent outcome (Dorflinger *et al. Urology*, **27**, 569–573, 1986; Jensen *et al. Scand. J. Urol. Nephrol. (Suppl.)*, **114**, 63–86, 1988; Neal *et al. Br. Med. J.*, **299**, 762–767, 1989). The authors' study of 37 men studied before and after operation contributes little to this debate because they offered operation only to men with low flow rates or high urethral resistance and cannot therefore know how well the others might have done. They may be correct in expressing the opinion that flow rate measurement is a useful adjunct to a careful history, particularly in highlighting those worrying men whose symptoms of urgency and frequency are dominant and whose flow rates are high or whose voided volumes are

low, but their study enables them neither to support nor to refute this opinion.

Yours faithfully,

D. E. Neal

Department of Urology, Freeman Hospital, Newcastle upon Tyne.

Reply by J. McLoughlin et al. We thank Mr Neal for his interest in our article.

He has commented that it would be incorrect to distinguish between high pressure/low flow and low pressure/low flow states on the basis of flow rates alone. A careful appraisal of the text will show that we are in complete accordance with his view and indeed have referred to the work of Blaivas (*Urology (Suppl.)*, **32**, 5–10, 1988) in the introduction and discussion to illustrate this point.

In addition he has stated that the important question is whether men with higher flow rates and typical symptoms of outflow obstruction do any worse following prostatectomy than those with low flow rates and symptoms. In this study we deliberately excluded men with high flow rates as our primary aim was to assess what proportion of men with low flow rates had evidence of an arbitrarily defined parameter of obstruction in order to evaluate how this predicted symptomatic outcome following prostatectomy. This we felt was of interest as a large proportion of urologists would have either conventional cystometry or just a flow rate machine which they use to evaluate men presenting with such symptoms as out-patients in an everyday clinical setting.

Symptomatic men with higher flow rates are indeed of interest because if it is possible to demonstrate that such men do equally well symptomatically as those with low flow rates then the whole question of pre-operative flow rate evaluation would need to be reconsidered. This question we are presently addressing with an ongoing prospective study, the results of which we hope will be available within the next 18 months.

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Subcommittee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons

Autumn Meeting: Royal Surrey County Hospital, Guildford. 4 and 5 October 1991

The Day Meeting of the Association on 5 October will be preceded by a post-graduate education session on 4 October, when the topic will be "Can Urologists Manage?"

Further information from: BAUS Secretariat, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Surgery in the Third World

Sir Ian Todd, past President RCSI, is anxious to build up a list of surgeons in all specialties from the United Kingdom and Northern Ireland (active or recently retired consultant, or higher surgical trainee) who would like to spend some time working and teaching in a third world country.

In most cases accommodation and subsistence are provided and in some air fares also. Periods abroad vary from 1 month upwards but 3 to 6 months are usually preferred.

Please write to Sir Ian Todd, KBE, FRCS, care of the Overseas Doctors Training Scheme Office at the Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN.

Diary

1991

- August 21–23 Edinburgh Urological Festival. Contact: Urological Festival Secretary, Department of Surgery/Urology, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU.
- August 22–24 Nordic Association for Andrology. Nordic Symposium on Epididymis and Annual Meeting, Sønderborg, Denmark. Contact: L. Linnet, Department of Surgery K, Sønderborg Hospital, DK-6400 Sønderborg, Denmark.
- August 25–31 First Urology Summer Forum, Oosterbeek. Contact: Secretariat Organization, PO Box 226, 3830 AE LEUSDEN, The Netherlands.
- September 1–6 6th World Congress in Ultrasound, Copenhagen. Contact: Spadile Congress Service, Sommervej 3, DK-3100 Hornbaek, Denmark. Tel: 45 2 20 24 96.
- September 2–3 A Comprehensive Approach to Nocturnal Enuresis, Nottingham. Contact: Caroline Roney Medical Conference Organisers, Congress House, 65 West Drive, Cheam, Sutton, SM2 7NB.
- September 4–7 Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllői ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.
- September 16–19 Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China.
- September 23–25 16th Annual Meeting of the International Urogynaecology Association, Sydney, Australia. Contact: Conference Secretariat, International Professional Travel P/L, Suite 103, 135 Macquarie Street, Sydney, NSW 2000, Australia.
- September 26–27 Annual Paediatric Urology Course, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
- October 3–5 Prostate Cancer and Urothelial Cancer; Controversies in Diagnosis and Treatment, Orlando, Florida. Contact: Imedex U.S.A. 1060 Cambridge Square, Suite D, Alpharetta, Georgia, U.S.A.
- October 3–5 Annual Meeting of Swiss Society of Urology, Geneva, Switzerland. Contact: Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.
- October 4–5 Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office.
- October 9–12 1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands.
- October 10–12 International Continence Society, 21st Annual Meeting, Hannover. Contact: Guus Kramer, Chairman ICS, Department of Urology, Hannover Medical School, P.O. Box 610180, 3000 Hannover 61, Germany.
- October 18–19 Surgical Treatment of Prostatic Cancer: Comparison of Techniques. Milan, Italy. Contact: Dr F. Gaboardi, Divisione di Urologia, Ospedale Fatebenefratelli ed Oftalmico, C.so Porta Nuova 23, 20121 Milan, Italy. Tel. 0039-2-636443.

October 20–
November 4 Royal College of Surgeons of England Joint Meetings in Pakistan and India. Contact: Craig Duncan, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, WC2A 3PN.

November 15–16 Third Biennial Asia-Pacific Meeting on Impotence, Taipei, Taiwan, R.O.C. Contact: Third Biennial Asia-Pacific Meeting on Impotence, c/o Taiwan Conference Management Co. Ltd, P.O. Box 68–439, 6F–3, 102 Chung Shan N. Road, Sec. 2, Taipei, Taiwan, R.O.C.

November 21 Controversies in the Management of Prostatic Cancer, St Bartholomew's Hospital. Contact: Dr A. Jelliffe, NETRHA, 40 Eastbourne Terrace, London, W2 3QR. Tel: 071 262 8011.

November 22–23 International Pelviureteric Junction Obstruction symposium, Stratford-on-Avon. Contact: Mr P. Shridhar, Department of Urology, George Eliot Hospital, Nuneaton CV10 7DJ.

1992

January 10 Final date for submission of abstracts for the 1992 BAUS Annual Meeting.

March 8–13 19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.

March 19–21 Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.

April 9–11 6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.

May 6–8 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.

May 10–14 American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.

May 24–28 Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.

June 10–12 Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.

June 23–26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.

June 22–25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.

July 22–25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.

August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

Mr Alec William Badenoch, MD, ChM, FRCS

Alec Badenoch was born on 23 June 1903 in Banff, Scotland. After school in Banff he proceeded to university in Aberdeen to study medicine following a preliminary MA in English Literature. At university he was captain of swimming and represented the university at tennis. After qualifying in 1927 he obtained his MD thesis in 1929 and the FRCS Eng. in 1934. He was appointed RSO to St Peter's Hospital, London in 1935 and in 1938 became Consultant Surgeon to the Metropolitan Hospital, London. Already in the RAF VR, he commenced active service in 1939 yet found time to complete work for his ChM degree, which he obtained from Aberdeen in 1945.

Between 1945 and 1950 he was appointed Consultant Surgeon to St Bartholomew's Hospital, St Peter's Hospital, King Edward VII Hospital for Officers, The Royal Masonic and The Samaritan Hospital for Women. He developed an international reputation as a urological surgeon and established the Department of Urology at Barts against considerable resistance from general surgical colleagues. His breadth of interest within urology was crystallised in his excellent "Manual of Urology", published in 1953 and completely rewritten in 1974. He refined the retropubic prostatectomy and developed his unique "pull through" operation for urethral stricture.

Within BAUS he was Honorary Secretary from 1951 to 1954, Vice-President in 1965 and President from 1967 to 1969. He was awarded the St Peter's Medal of the Association in 1974. He was a member of the Council of the Royal College of Surgeons, became a Patron and was awarded a Hunterian Professorship in 1948. He was President of the Urological Section of the Royal Society of Medicine, Co-founder of the European Association of Urology and was the British delegate to the International Society of Urological Surgeons for many years. He undertook many Visiting Professorships and travelled widely, particularly in the



USA, where he was made an Honorary Member of the American Association of Urology and a member of the GU Surgeons.

He was tremendously supported in all he did by his wife Jean, also a medical graduate, who assisted him in so many ways.

Alec died, aged 87, on 16 February 1991.

He is survived by his wife Jean and two sons, one of whom (David) is a Consultant Urologist to the Royal London Hospital. His eldest son John was killed in a car accident.

His many friends will miss his familiar figure at BAUS meetings, where he was an assiduous attender until the last few years.

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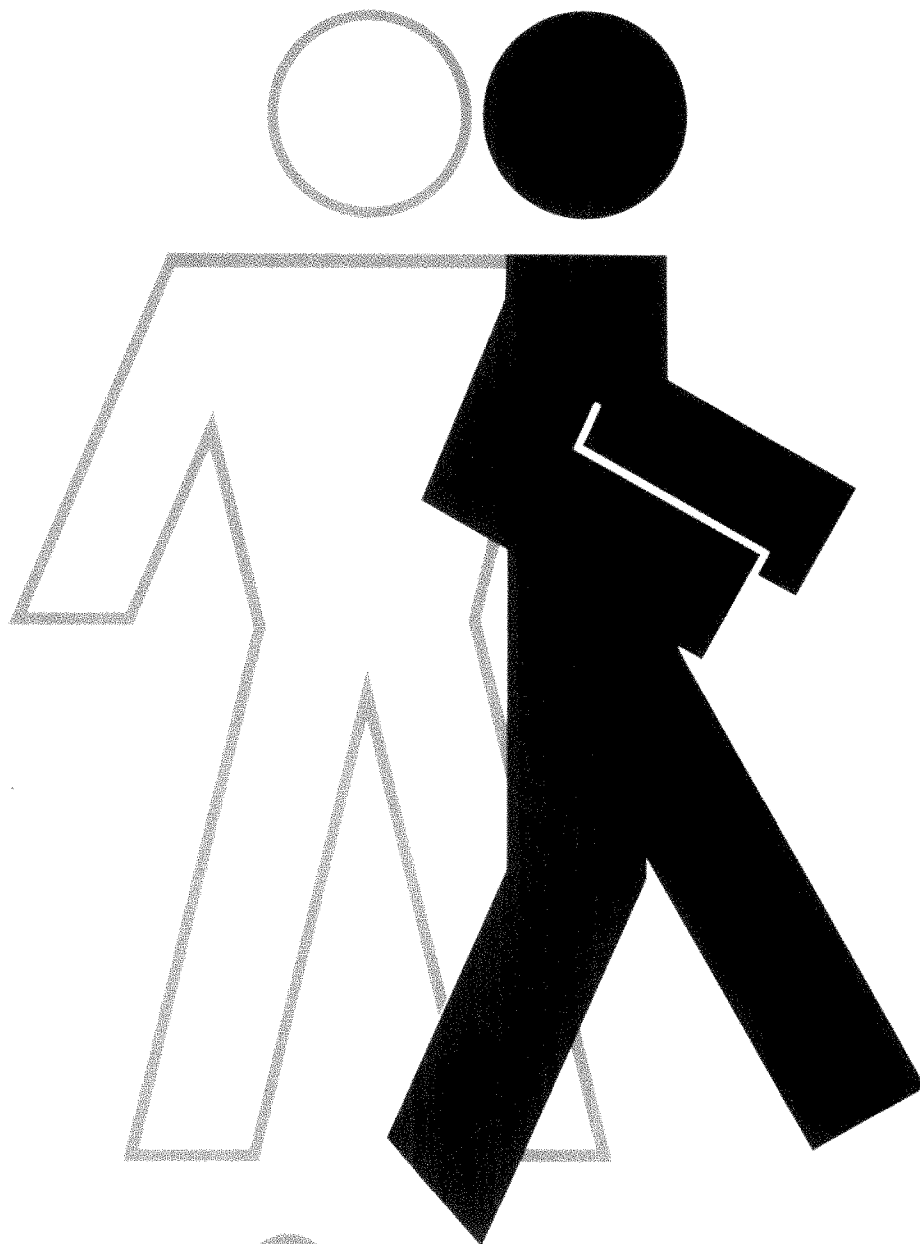
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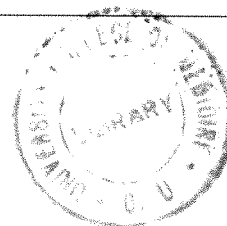
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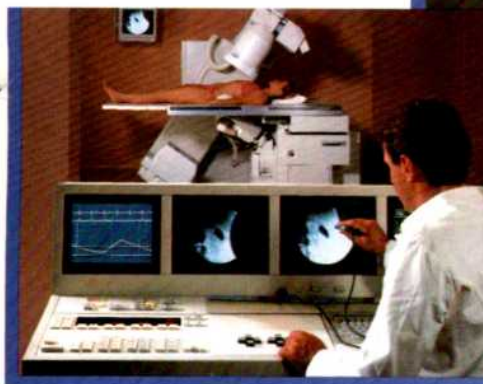
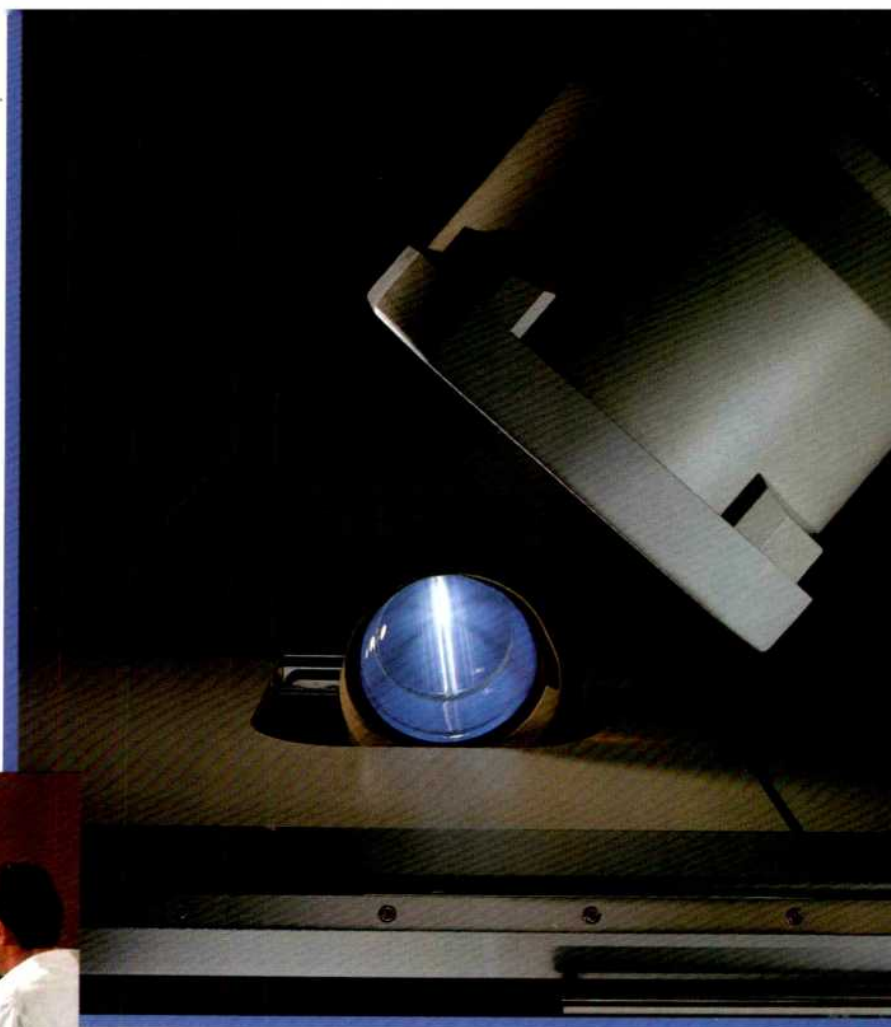
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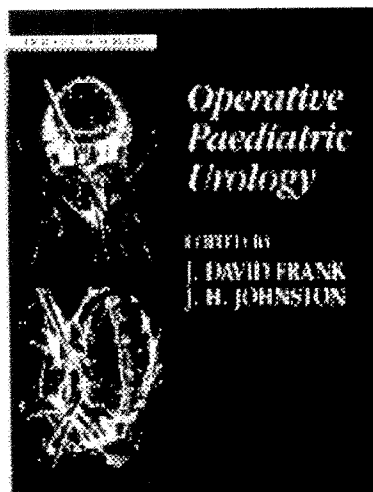
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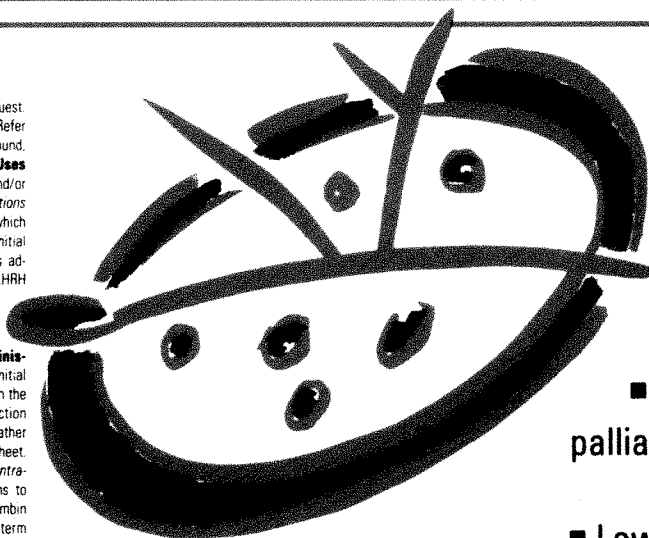
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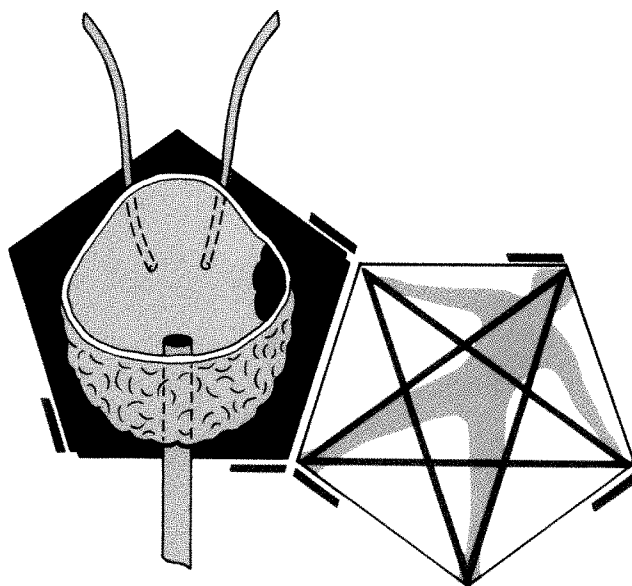
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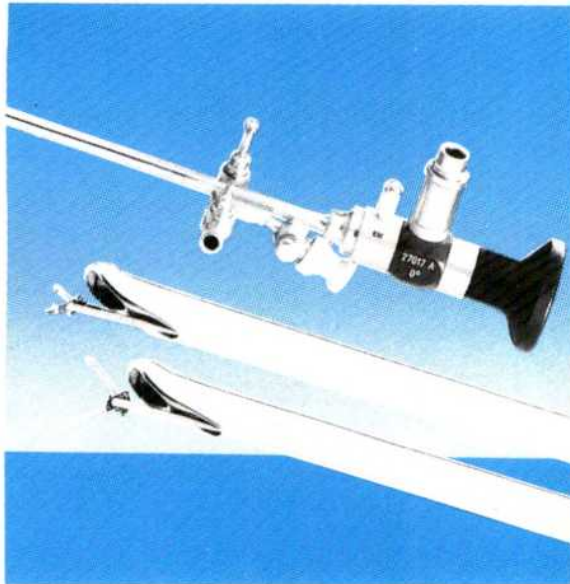
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British Journal of Urology	0007-1331	12	January	
British Medical Bulletin	0007-1420	4	January	
Cell Calcium	0143-4160	10	January	
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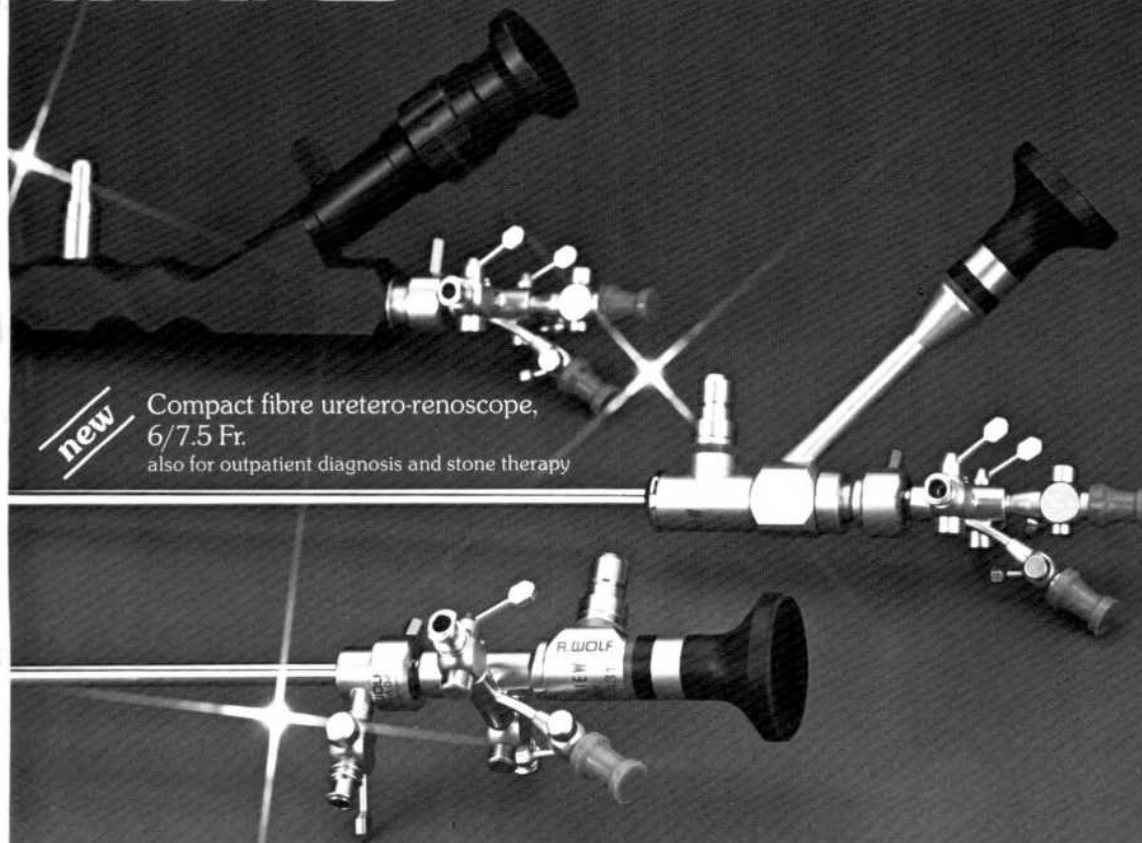


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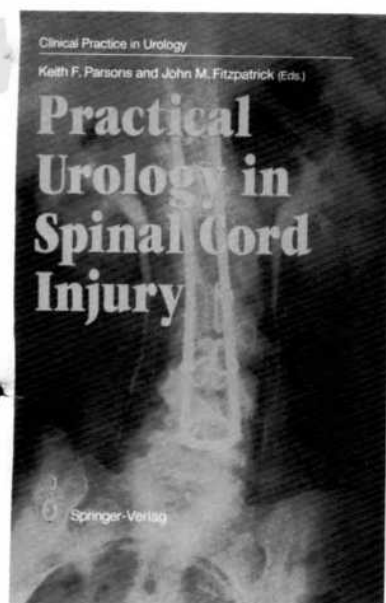
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K. F. Parsons, University of Liverpool; J. M. Fitzpatrick, University of Dublin (Eds.)

Practical Urology in Spinal Cord Injury

1991. XII, 145 pp. 14 figs. (Clinical Practice in Urology)
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Here is an easily readable account of a complex topic that has previously been kept to the academic "higher ground". The editors have solicited contributions from specialists experienced in treating urological disorders in spinal cord-damaged patients. The result is a book with didactic and practical guidelines on both the acute and long-term management of patients. All of the problems presented are common ones. For example: the inability to void, urinary tract infections, upper tract dilatation and sexual activity. The book gives definite advice on how to manage such problems and which investigations are the most appropriate.

The need for this work is apparent: it is largely because of detailed attention to the urinary tract that the life expectancy of spinal cord-damaged patients has been increased and their quality of life improved.

P. M. Hanno, D. R. Staskin,
R. J. Krane, A. J. Wein (Eds.)

Interstitial Cystitis

1990. XVI, 218 pp. 52 figs. 22 tabs.
Hardcover DM 153,-
ISBN 3-540-19598-X

This monograph presents an overview of the increased clinical and basic research on interstitial cystitis, a urologic disorder which is much more common than was ever believed in the past. The authors have contributed chapters on its epidemiology, etiology, diagnosis and management.

J. O. Drife, Leicester; P. Hilton,
University of Newcastle upon Tyne;
S. L. Stanton, London (Eds.)

Micturition

1990. XIV, 356 pp. 101 figs. Hardcover
DM 180,- ISBN 3-540-19614-5

The contributions in this book emphasize the areas of current controversy in the rapidly developing field of urogynaecology. Experts discuss the morphology, physiology and investigation of dysfunction of the lower urinary tract. In particular, the management of genuine stress incontinence, detrusor instability and voiding disturbances are addressed.

T. A. McNicholas, London (Ed.)

Lasers in Urology

Principles and Practice

1990. XII, 168 pp. 63 figs. (The
Bloomsbury Series in Clinical Science)
Hardcover DM 178,-
ISBN 3-540-19615-3

This book covers the field of laser urology as currently practiced, particularly with regard to bladder cancer, ureteric and urethral tumours and the endoscopic laser destruction of stones. There is a comprehensive how-to-do-it section for each technique with much practical advice on how to use lasers.

I. Rocker, Newport, UK (Ed.)

Pelvic Pain in Women

Diagnosis and Management

Foreword by L. P. Thomas
1990. XIII, 171 pp. 32 figs. Hardcover
DM 120,- ISBN 3-540-19594-7

This is a practical handbook which discusses the diagnostic criteria and treatment of a common problem: female pelvic pain.

E. K. Lang, Louisiana State University,
New Orleans (Ed.)

Radiology of the Upper Urinary Tract

Foreword by M. W. Donner,
F. H. W. Heuck

1991. Approx. 385 pp. 418 figs. 13 tabs.
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This instructive volume is exceptionally comprehensive in that it covers all aspects of radiologic diagnostic techniques in the upper urinary tract.

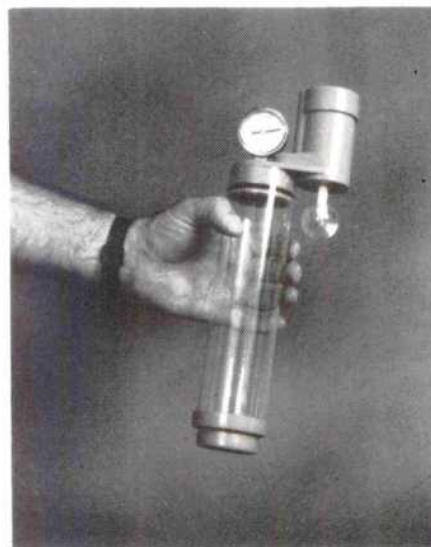
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REVIEW

The Application of Information Technology in Urology

E. S. GLEN

Walton Urological Teaching and Research Centre, Southern General Hospital, Glasgow

To compute or not to compute is hardly the question. When and how, that is another matter. Information technology (IT) pervades everyday living. School children use computers from an early age and there is clear evidence that learning is enhanced when suitable programs are used. Initially reluctant to consider the application of computers, I became better informed when my son acquired a Sinclair ZX81 (Glen, 1983).

The medical profession continues to debate the use of computers. Terminology can be difficult. For example, "VT under MS windows offering ICL VT facilities, standard expected windows features like cut and paste, standard user interface, mouse support and reduce session to an ICON"—not the most approachable or attractive of texts, but a typical example of an advertisement in IT literature. However, the requirements of the White Paper "Working for Patients (CM 555)" make the use of IT essential and this need has been recognised by the government. If we are to maintain and develop our clinical services we must participate in resource management and in audit (both clinical and financial), in addition to dealing with a heavy clinical workload. Urologists see more new patients than ever before and discharge patients earlier, thus increasing the need for improved communication.

Those of us directly involved in the medical advisory structure and in management are aware that there are different motives for collecting and analysing data. More than ever, clinicians require access to accurate data affecting clinical needs in order to preserve the correct balance between rationalisation, economy and efficient clinical practice including research. For this we need computers.

Why does antagonism to IT remain? Inability to use a keyboard and the mistaken belief that it is necessary to understand computer language are major factors in discouraging newcomers. Do not be put off by the instruction books or computer jargon. For example, the manual for the first Apple computer was written in the most cumbersome style but hidden towards the back was a 2-page summary which proved sufficient for our initial needs. If you can program, or are prepared to learn, so much the better, but it is unnecessary to do so with the increasing range of commercially available versatile programs.

The best computer system remains the human brain. Computing and the various forms of IT provide essential help if we are to cope with the increasing volume of information and documentation. IT is ideal for fact and number "crunching" and also for repetitive tasks. The correct application of IT can release the clinician and supporting staff from basic work and analysis, and so provide more time and better facilities for clinical care, audit and research. The most recent systems combine multiple facilities, including TV and video imaging, sound, graphics, filing and word processing as well as providing responsive teaching and self-assessment programs. Tables 1 to 3 outline the present and future ranges.

Until recently, administrators and providers of finance in the UK have limited their interest to central mainframe computers. This has inhibited the development of user-friendly local systems. Some hospitals have mainframe-driven patient administration systems (PAS) which are invaluable for providing basic data. These systems can provide terminals at both clinic and ward levels and some are flexible enough to provide information and analysis for managerial and clinical audit. However, many of these systems attempt too much and

Table 1 Range of Available IT Activities

<i>Patient Administration Systems (PAS)</i> : Employ central mainframe computer invaluable for basic patient data. Capable of servicing local work stations but systems can be restrictive and unwieldy. Still under development.
<i>Data Collection, Storage and Analysis</i> : Many enthusiasts have developed programs well suited to their own departments. These and commercially available programs for PCs are listed in the West Midlands Guide. Still too much emphasis on rigid central mainframes.
<i>Word Processing</i> : (1) Routine correspondence, including standard letter, reports and theatre notes. (2) Preparation of manuscripts.
<i>Audit</i> : PCs equipped with word processing, statistical and other appropriate programs are invaluable, e.g. waiting list management.
<i>Clinic Appointments and Recall Programs for Follow-up</i> : PC and mainframe programs are available.
<i>Teaching and Self-assessment Systems</i> : Still under development, e.g. AUA programs.
<i>Central Computerised Reference Facilities</i> : (1) Literature search. (2) Advisory Bureaux.

Note: Initial emphasis on costly central mainframe systems has impeded implementation and standardisation of the many programs developed on PCs by enthusiasts. The IT industry has now recognised the need for change and the Health Authorities must follow suit.

Table 2 Examples of In-house Programs in Routine Use

-
- | |
|--|
| (1) Standard letters and guidance leaflets. |
| (2) Immediate discharge and prescription summaries. |
| (3) Formal detailed discharge letters incorporating summaries. |
| (4) File of department summaries for ready recall. |
| (5) Urodynamic graphic recording and generation of report letter including guidance leaflets. |
| (6) Patient-operated history-taking producing printouts of history and indicated investigations. Supplies a copy to patient, GP and for records. |
-

All of these programs are included in the references.

are cumbersome. Now, even International Computers Ltd (ICL) has recognised that enthusiasts, including clinicians, have developed valuable local systems capable of integration. At the end of May 1990, ICL announced a change of policy and for the first time advocated the use of high powered personal computers (PC), producing one at very reasonable cost. This does not preclude centralisation of data storage and analysis. PCs providing local functions can be formed into clusters or networks which feed into a central mainframe

Table 3 Futuristic Applications Available or Under Development

<i>Optical scanning and optical mark reading (OMR)</i> : For rapid storage of data without recourse to keyboard. Functions: (1) Storage of medical records. (2) Handling of questionnaires, e.g. Bloomsbury H.A. self-completion patient satisfaction assessments. (3) Handling of manuscripts, e.g. Journal of Royal College of Surgeons initiative extending use of desk top publishing.
<i>Image recording</i> : It is possible to store X-rays, scans and pathology illustrations alongside text. Uses: (1) Space-saving long-term comprehensive storage of medical records for routine, audit and research purposes. (2) Education.
<i>Teaching Aids</i> : Several systems are in use. Examples: (1) AUA programs for self-assessment. (2) Professor Lardennois' comprehensive audiovisual interactive programs used in Reims.
<i>Vocal input</i> : Programs accessed by voice are in use, e.g. voice recognition patterns used by security in intercepting radio transmissions. Medical applications are awaited.

computer. If the central computer fails, local functions can continue. Until recently, progress has been slow and patchy (Rose, 1990). ICL's change of emphasis will strengthen the increasing demand for powerful local facilities.

When I asked experts for advice, the usual comment was that I should wait until better machines and programs became available. Superficially, this appears sound advice but do not be put off by it. If you are a realistic enthusiast, or have contact with one, begin with the best and most flexible system that can be obtained with the money available to you. Visit a clinical department active in Information Technology, explore what is available, determine whether the programs have anything to offer you and ensure that they are easy to adapt to your own particular needs. The cheapest option may not be the best in the long term, although many programs have been created on relatively inexpensive machines. It is important to make a start. Our funding system in the UK tends to discourage initiative, but can be made to respond if pilot studies give encouraging results. If possible, the system should be compatible with other systems in your hospital.

The recently established consortium X/Open, consisting of 20 members committed to open compatibility, has encouraged rapid expansion of versatile programs. This consortium appears to have widespread support, including government

institutions in a number of countries. If the venture is as good as it appears to be, many existing problems of cross communication will soon be eradicated.

Some functions, such as urodynamics, may be so specialised that compatibility is relatively unimportant in the first instance (Eadie *et al.*, 1986). Use the NHS Register of Computer Applications*, check the market, but beware of the hard sell. Also beware of the unrealistic enthusiast promoting a project that offers little in relation to your needs. For the small systems, maintenance contracts (running at about 15% of the purchase cost) are probably an unnecessary expense. Development is so rapid that your first system should almost be regarded as a disposable item to be used for learning and development, subsequently to be replaced if it fails or when better systems become available.

Equipment (hardware) ranges from electronic typewriters with limited memory through dedicated (and therefore limited function) word processors, to PCs capable of many functions. Urologists are more likely to benefit from a PC with its greater potential, adaptability and ability to be linked to a cluster or network such as one of the patient administration systems. Modern PCs and printers are extremely good value and a suitable package, including a word processing program, can be obtained for less than £3000. Special functions may be met in stages as finances permit. Consult your local management, university or Health Board, who may have negotiated special terms in this competitive market. Seek advice about compatibility with existing or proposed systems but be prepared to go it alone if undue delay or interference is likely.

Audit

Audit is of growing importance and IT will be an invaluable aid. The British Association of Urological Surgeons (BAUS) has established a committee to explore available and potential systems capable of classifying and analysing the urological workload. The West Midlands Regional Health Board Authority, in collaboration with Anderson Consulting, has produced an excellent guide to PC-based medical audit systems (Computers in Medical Audit, 1990). This gives a well balanced account of available systems and provides an excellent glossary. Classification of diagnoses and procedures is proving difficult. The existing ICD and OPCS

systems cannot directly translate into diagnostic related groups (DRG). The West Midlands Guide lists many individual systems and a smaller number of commercial programs. Computers can facilitate the incorporation of individual coding systems by a process of "mapping back." The clinician or clerk enters the preferred key words or code. A suitable program can then match this with (*i.e.* "map back" to) the codes required by national professional bodies such as BAUS. Writing such a program will be time-consuming, and the fewer local variants the better, although standardisation will be difficult. The North Western Regional Health Authority has recently given early notice of 2 classifications presently being computed. Their work has been drawn from a full regional urology database, the DRG classification used in the USA, and ICD and OPCS coding manuals. The preliminary set of materials is awaited with interest and no little trepidation.

Waiting list management

Waiting list management can be facilitated by computing patient data, including condition, degree of urgency, estimate of theatre time required and proposed date of admission. Systems have been available for many years and can incorporate standard letters notifying admission dates and other information. Recall systems for the follow-up of conditions such as bladder carcinoma improve the efficiency of the urology service. It is regrettable that many urology departments do not yet have access to these systems.

Transmission of discharge summaries and letters

Transmission of discharge summaries and letters is a major problem. Articles and correspondence in the British Medical Journal have described some of the difficulties and offered some solutions. I am fortunate in having had enthusiastic physicists who have been able to design programs particularly suited to our special interests, and within the limited funding available. Programs have been developed to facilitate the production of ward level discharge summaries, including prescriptions of medication. The resident's handwritten summary has been replaced by a printout generated by the resident using a menu-driven program (Morrison *et al.*, 1991). When the final discharge letter is dictated and about to be printed, the secretary calls up the discharge summary from the database and modifies it where necessary in accordance with the dictated definitive information. The summary in this formal discharge letter is ideally suited for medical audit.

* Contact Joy Reardon, Regional Computer Centre, East Anglia Regional Health Authority, Union Lane, Chesterton, Cambridge.

Application of computers in direct patient management

Application of computers in direct patient management is more controversial. Our computerised history-taking program works well and has reduced clinic waiting times while expediting communication (Glen *et al.*, 1989). It provides potential for screening in the community during health promotion campaigns. It has been suggested that the program could be used to reassess patients on long waiting lists, updating priority where appropriate. In areas where a language problem exists, the system could be extended to include a variety of languages with a final printout in English and the chosen language. The program has also been useful in introducing medical undergraduates to clinical history-taking by illustrating the type of question that should be asked, the possible conclusions to be drawn and investigations to be suggested. Nothing will replace contact with patients, but additional practice is useful.

Our nursing colleagues are exploring the application of IT, *e.g.* for ward management. Programs exist for patients' daily records and the related nursing process. Medical notes could be entered in the same way, producing legible detailed records for the individual patient. Our experience with discharge and prescription summaries suggests that the quality of records and accountability improves when the end result is a legible computer printout. It is hoped that eventually there will be readily available printouts of patient management by doctor, ward or clinic. The need for financial billing caused the introduction of this type of system in American hospitals many years ago and the White Paper now provides a similar incentive here.

Management of records

Management of records needs to be improved and a start has been made in some departments. Inadequate provision for storage and retrieval of clinical records is virtually universal, affecting clinical practice, research and medico-legal needs. Some countries attempt to solve the problem by placing the responsibility on patients and relatives, and early UK experience of this has also been reported (Smart Card Monthly, 1990). There are major clinical and legal implications regarding time-limitation of access and litigation that are inadequately covered by current legislation. Medical and nursing records become increasingly detailed and therefore bulkier. The replacement of handwritten records by computer entries would facilitate subsequent culling and storage. Reports

and visual records of investigations such as X-rays, scans and histopathology show the same trend. IT will provide the solution.

Table 2 lists specific expanded applications. The first 4 are fairly well known, especially to those with hospital PAS facilities. Anyone with access to word processing can use standard letters, reports and theatre notes. General use of standard text in word processing will become more popular as a result of improved programs. Manipulation of text is easy and well within the ability of any typist, even the medical amateur.

Future applications

Bar-coding and optical disc scanners should be considered. There is national concern about the reducing pool available for recruitment of secretaries and records staff and the added problem that Health Service pay compares unfavourably with pay in the private sector. Without IT, the position can only deteriorate and we are a long way from having the necessary funding and expertise to fill the gap. France and Italy are already at a more advanced stage, as was seen at the First European Conference on Informatics, Teaching and Urology in November 1989. (Informatics is the European term for IT).

The Health Service must use the best of the existing systems and generate improvements where necessary. At the recent annual meeting of the Urological Computing Society in Glasgow, Professors Lardennois and Marandola gave an interesting account of a wide range of expert systems, including the use of video in computer programs for teaching and research. Unfortunately, Britain lags behind Europe.

The Standing Committee on Postgraduate Education of BAUS Council is to be congratulated on its initiative in encouraging the Urological Computing Society to run its first teaching course in March 1990. The second course will be held in Glasgow in 1991 and the author welcomes enquiries, comments and suggestions.

Acknowledgements

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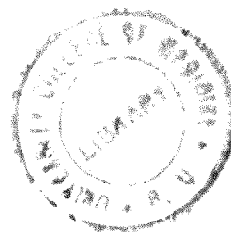
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Experience with Sperm Counts Following Vasectomy

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Summary—The records of Aberdeen men requesting vasectomy between 1978 and 1981 were studied and a sample of men were interviewed about 3 years after the operation; 85% completed the standard requirements for seminal analysis and were given the "all clear"; two-thirds were cleared after sending 2 samples and usually within 20 weeks after vasectomy; 10% of men sent at least 1 sample but were never cleared and the remaining 5% ignored the requirements. Information from 70 men (63 interviews, 7 questionnaires) gave some indication of reasons, often multiple, for incomplete or non-compliance; these included embarrassment, ambiguous feelings about having more children, inadequate understanding of reproductive physiology and blind faith in the surgeon.

Vasectomy has the disadvantage that it is not immediately effective. For maximum protection against pregnancy, men are usually advised to obtain 2 consecutive negative sperm counts before abandoning other contraceptive methods. It has been reported that most men achieve azoospermia within 6 months (Barnes *et al.*, 1973) but we are unaware of published reports on what may be involved and why some men do not comply with the requirements for seminal analysis. Some information on these aspects was provided in a study of male and female sterilisation in Aberdeen (Thompson *et al.*, 1987).

Patients and Methods

Men who requested vasectomy between 1978 and 1981 were referred to urological or general surgeons by their family doctors. With the appointment letter from the hospital, they were sent a form to complete giving demographic and family information. Those men who were resident in Aberdeen City District and who requested vasectomy for contraceptive reasons only ($n = 612$) were informed of the study by the consultants and, if agreeable, their details were passed on to the research team. Refusals were negligible. In due course a random

sample of the men (1 in 4 increased to 1 in 2 when numbers were less than expected) was contacted to arrange interviews with them and their wives at home, before the operation. At this stage 15% withdrew for personal reasons or on account of working commitments. Of the 154 men who were willing to participate, 70 had already had the operation when contacted. Thus 84 men were interviewed and followed up 3 years later, when it was found that 82 had had a vasectomy; 2 men had not had the operation, 1 because he separated from his wife and the other on medical advice and so his wife had been sterilised instead.

Since so few men withdrew from the waiting list, the number of men requesting vasectomy can be taken as similar to those who had the operation. There was no significant difference between the sample interviewed and all men requesting vasectomy in respect of age, occupation, duration of marriage and family size (Thompson *et al.*, 1987). In comparing experiences with sperm counts, for practical reasons, only details of a random sample of 1 in 2 men who had a vasectomy ($n = 284$) were compared with the interviewed sample.

Not all 82 men who had been interviewed before having a vasectomy were available for interview 3 years later; 63 were seen, together with their wives, and 7 who were living or working away from Aberdeen completed a questionnaire. Of the remaining 12 men, 2 had left Aberdeen and did not

return the questionnaire, 3 refused to be interviewed, 2 had died and 5 could not be traced. Records of the number and results of samples received from each man were available from the Regional Cytology Service, and for those men interviewed their accounts were compared with these.

There was a standard procedure for seminal analysis organised by the Regional Cytology Service. Three months after vasectomy the man was sent a kit containing a specimen jar with instructions for its use and a pre-paid envelope for its return. If there was no response the family doctor was informed. The result of the sperm count was sent to both the consultant and the family doctor. A month later the procedure was repeated. If both counts were negative, this was taken to mean that the man was "all clear" and that it was safe to abandon other methods of contraception; there was no further follow-up. If the specimen continued to contain spermatozoa, the consultant advised on further action to be taken. The study showed that the routine computerised recall system and standard procedure worked well.

Results

According to the hospital records, the interviewed sample was similar to the population sample, in so far as about 85% of men followed the requisite procedure until they were given the "all clear" and about 5% sent no samples; the remainder sent some samples but did not complete the requirements (Table 1). About two-thirds of the men sent 2 samples and about one-tenth sent 4 or more (Table 2).

In the population sample, 86% of men complied fully with the requirements and received the "all clear". This applied to 84% of the interviewed sample. Considering only those who eventually

Table 1 Results of Sperm Counts for Interviewed Sample and 1 in 2 Sample of Vasectomy Population

	<i>Interviewed</i>		<i>Population</i>	
	<i>No.</i>	<i>(%)</i>	<i>No.</i>	<i>(%)</i>
Given "all clear"	69	(84.3)	244	(85.9)
Some samples sent but not cleared	9	(10.9)	25	(8.8)
No samples	4	(4.8)	15	(5.3)
Total	82	(100.0)	284	(100.0)

$\chi^2 = 0.3339$ df 2 NS

Table 2 Number of Semen Samples provided by Interviewed Sample and 1 in 2 Sample of Vasectomy Population

<i>No of samples</i>	<i>Interviewed</i>		<i>Population</i>	
	<i>No.</i>	<i>(%)</i>	<i>No.</i>	<i>(%)</i>
0	4	(4.8)	15	(5.3)
1	4	(4.8)	19	(6.7)
2	54	(66.3)	187	(65.9)
3	11	(13.3)	31	(10.9)
4	4	(4.8)	18	(6.3)
5-8	5	(6.0)	14	(4.9)
Total	82	(100.0)	284	(100.0)

$\chi^2 = 1.0894$ df 5 NS

received the "all clear", the interval after vasectomy varied, mainly depending on how promptly they had complied with the request for samples. The mode was 18 weeks; about 20% were cleared in less than this time but for about 5% it took 40 or more weeks (Table 3).

Follow-up of the interviewed sample took place 2½ to 3 years after the operation and with this lapse of time, many of the men were vague in discussing what they found to be a very embarrassing subject. The wives were often more specific about what had happened since they had often been responsible for posting the samples and phoning for the results; also, clearance had usually meant that they could stop taking the pill, on which most couples relied.

Of the 70 men who were interviewed or who completed a questionnaire, 58 had complied with requirements and been given the "all clear" after 2 consecutive sperm-free samples, 8 men had provided at least 1 sample but had never been cleared, and the remaining 4 had sent no samples.

Table 3 Interval between Vasectomy and "all clear" in Men who Completed Requirements in Interviewed Sample and 1 in 2 Sample of Vasectomy Population

<i>Completed weeks</i>	<i>Interviewed</i>		<i>Population</i>	
	<i>No.</i>	<i>(%)</i>	<i>No.</i>	<i>(%)</i>
<17	3	(4.4)	13	(5.3)
17	11	(16.2)	31	(12.9)
18	18	(25.0)	47	(19.4)
19	14	(19.2)	36	(14.6)
20-22	6	(8.8)	38	(15.4)
23-26	9	(13.2)	31	(12.9)
27-39	6	(8.8)	35	(14.2)
40+	3	(4.4)	13	(5.3)
Total	70	(100.0)	244	(100.0)

$\chi^2 = 4.88$ df 7 NS

Samples sent but no "all clear"

The reasons the 8 men gave for not completing requirements for semen analysis varied to some extent according to the number of samples they had provided, which ranged from 1 to 5.

According to the records, 3 men had sent only 1 sample, although 1 man thought he had sent 2. Embarrassment had deterred 2 of these 3 men. One had sent a sample a year after vasectomy under pressure from his wife, who was terrified of becoming pregnant; as the sample was negative and so much time had elapsed the husband thought it was unnecessary to send another sample, but his wife was unhappy about this and only had a coil removed 2 years later because of infection. Overcoming his embarrassment, 1 man sent 1 sample but when the second was due he was ill and ignored it; he said he trusted the surgeon "to do his job properly" and doubted the need for such checks. The third man and his wife, who had been intermittent users only, abandoned using contraception several weeks before vasectomy, leaving the possibility of pregnancy "to fate"—they said that they would prefer it to be "God's will" whether they had another pregnancy or not.

Three men had provided 2 samples. Two of them did not fully understand the reason for the procedure and felt that they had complied in providing 2 samples. One man, as the second result was negative, decided that he had done enough although he had never been cleared. Both samples provided by the other 2 men had been positive, but whereas 1 put his faith in the surgeon the other had some reservations about whether he had done the right thing and after abstaining for a time decided to chance having another pregnancy.

One man had provided 3 samples which were all positive. He and his wife gave a very confused report and could not agree on the number of samples sent, the results and whether they had ever received the "all clear".

One man had provided 5 samples and reported that after 6 months he had been given the "all clear" by his family doctor, although the records showed 3 positive results, a sample with "a few sperm" and 1 negative result only.

No samples sent

The reasons why 4 men sent no samples were varied and often multiple. Two men, disgusted at the idea of masturbating, had refused to provide any samples. However, 1 of these men and his wife said that they had been quite happy to chance having

another baby, which might have given them a mixed family. The second man had risked intercourse without contraception after 3 months, based on when a neighbour had been given the "all clear".

The other 2 men, who had sent 2 samples, did not express similar feelings of disgust. One thought that seminal analysis was unnecessary for him as his wife was 2 months pregnant when he had the operation. The second man and his wife had second thoughts about the finality of sterilisation when 1 of their children was seriously ill soon after the man had a vasectomy and they decided to chance having another pregnancy.

The significance of having a concurrent operation with vasectomy and incomplete compliance is uncertain. The 2 men in the interviewed sample who had a concurrent hernia repair did not complete the requirements, which seemed to be associated with an extended post-operative period of abstinence and blind faith in the surgeon.

Being given the "all clear" was no absolute guarantee, as 1 couple discovered to their distress. After 2 negative results they were cleared 19 weeks after vasectomy, but the man experienced recanalisation of the vas, his wife became pregnant 4 months later and the pregnancy was terminated.

The 12 men who did not complete requirements ranged in age from 29 to 41 years and their occupations covered the whole range from professional to general labouring; in these respects they were fairly representative of the vasectomy population. Such small numbers do not allow detailed analysis.

Discussion

Most men complied with the sperm count procedure and for the majority it was straightforward—they provided 2 samples of semen which were negative well within 6 months. Receiving the "all clear" was more protracted for those who had positive results and were required to provide additional samples or for those who delayed sending samples, either because they were working away from home or for personal reasons.

Reasons for failure to comply with the standard procedure for seminal analysis varied and were often multiple but can be considered under certain headings.

(a) *Embarrassment.* The overt or underlying reason for most of the men was embarrassment. Although they usually accepted that it was necessary to provide the samples and they overcame any

embarrassment, helped by the procedure being "treated in such a matter-of-fact way that it was reasonably clinical", a few were deterred by the idea of masturbating.

(b) *Ambiguous or uncertain feelings about having more children.* Faced with the finality of sterilisation, a few couples preferred to let fate take its course and were not concerned with compliance. However, the interviews showed that taking chances before being cleared was by no means restricted to these couples.

(c) *Absolute trust in the surgeon.* The reputed success of vasectomy led a few men to place absolute trust in the surgeon and so to think that any checks were superfluous.

(d) *Inadequate understanding of reproductive physiology.* The significance of having 2 negative samples was not always appreciated. Also, some couples believed that with the passage of time infertility was inevitable.

This study has highlighted a lack of understanding about reproductive physiology (both male and female) and such ignorance is of particular concern when it leads to non-compliance with seminal analysis requirements. It was evident that the practice of family doctors and surgeons in imparting information varied; thus some men felt that consultations had been unnecessarily duplicated and others reported that they had received little explanation from anyone. The majority, however, said that they had been given information by either the family doctor or the surgeon and they assumed that this was the arrangement decided between the doctors. The men sometimes volunteered that they were "too uptight" when attending hospital to be receptive to what they were told and found it advantageous if consultations included their wives. Doctors' explanations with diagrams had often provided the first real understanding of what was involved in vasectomy but never seemed to include discussion of female sterilisation, the differing aspects of which still puzzled some couples. Simple explanatory leaflets which some family doctors and surgeons provided, or those obtained from Family Planning Clinics which they could keep and read at leisure, had been greatly appreciated.

Although the men reported much discussion

amongst friends and "mates" about the operation *per se*, and the requirements of seminal analysis were generally known, they felt that the subject of intercourse was avoided and largely neglected by the doctors. Most men had felt too embarrassed to ask but those who had made enquiries reported very mixed advice. Few seemed to have been told "as soon and as often as possible in order to get rid of the bank of sperm". In fact the evidence showed that the frequency of intercourse usually fell after vasectomy but increased once the couple had been given the "all clear".

In order to ensure that no man, whatever his apparent knowledge, is left in ignorance, we suggest that all couples should be given leaflets explaining in simple terms (with diagrams) exactly what vasectomy involves, details of the procedure, reason for seminal analysis and specific advice about intercourse after vasectomy. This should reinforce personal explanation, preferably with sketches, by medical or other designated staff as a routine. The men should also be given the option of having their wives present at any consultation.

Acknowledgement

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Cystine Stones: The Impact of New Treatment

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Summary—The hardness and frequent recurrence of cystine stones present a special challenge to the urologist. In this study, 15 cystinuric patients (11 males, 4 females; mean age 36 years, range 17–54) were treated and followed up over a period of 30 months (range 2–40). Most patients had a previous history of open surgery. The diagnosis of cystinuria was confirmed by metabolic studies and infrared spectrometry of stones.

Over the follow-up period recurrence was observed in 23 instances in 11 patients, leading to 38 "stone treatments" on 74 cystine stones. The percutaneous approach was used alone in 9 cases and in association with extracorporeal shock wave lithotripsy (ESWL) in 9 cases. ESWL was used alone in 18 cases. Medical treatment included high fluid intake, alkalinisation and Thiola (tiopronin, N-(2-mercaptopropionyl)glycine) in 6 patients. The overall stone-free rate assessed 3 months after treatment was 44.7%, which compares poorly with the rate for non-cystine stones. The recurrence rate is very high and instrumental treatment should not therefore be used excessively; it is indicated only for stones that are symptomatic or refractory to intensive medical therapy.

Cystinuria is an inherited autosomal recessive disease (Rosenberg *et al.*, 1966) characterised by abnormalities in the renal and intestinal cell transport of the basic amino acids cystine, ornithine, lysine, arginine and possibly cysteine (Crawhall *et al.*, 1969).

The relative insolubility of cystine in urine results in the formation of cystine crystals and calculi. The formation of cystine urolithiasis depends on urinary cystine excretion, urinary volume and urinary pH. The quantitative excretion of the poorly soluble amino acid depends on whether the disease is heterozygous or homozygous. The volume of urine in which the cystine is dissolved, urinary pH and the urinary solubility of cystine may be modified by medical therapy. The incidence of this disorder is approximately 0.05% of the general population and 1 to 4% of all patients with urinary stones (Thomas *et al.*, 1983).

The special crystalline structure of cystine stones means that they usually respond poorly to ESWL, ultrasound or electrohydraulic shock waves applied

percutaneously. They also have a high rate of recurrence despite medical therapy, and their management presents the urologist with many problems.

In this study the patients were selected over a short period of time and the methods and indications were homogeneous and standardised. The patients were treated by percutaneous lithotripsy (PCNL) or ESWL or both between 1984 and 1989.

Patients and Methods

From March 1984 to December 1989, 15 patients (4 women, 11 men; age range 17–54 years, average 36) were treated for obstructive or symptomatic cystine calculi. The diagnosis of cystinuria was confirmed by metabolic studies and chemical or crystallographic studies of stone fragments. Most patients had been treated previously by open surgery for urolithiasis (4 cystolithotomies, 22 nephrolithotomies, 2 partial nephrectomies and 1 ureterocaliceal anastomosis) or congenital abnormalities (1 congenital pelviureteric junction obstruction treated by pyeloplasty).

Changes in the renal parenchyma were present at intravenous urography (IVU) in 5 cases and the serum creatinine level exceeded $120 \mu\text{mol/l}$ in 4. Hypertension was present in 3 patients; 5 were on medical treatment (high fluid intake, urine alkalinisation and Thiola).

The patients were followed up over a mean period of 30 months (range 2–40). Recurrences were observed in 23 instances in 11 patients, leading to a total of 38 hospitalisations during which treatment by ESWL or PCNL or both was performed.

During these 38 hospital admissions a total of 74 cystine stones were observed. The stones were ≤ 10 mm in 35 cases (47%), between 10 and 20 mm in 21 cases (28%), between 20 and 30 mm in 14 cases (19%) and > 30 mm in 4 cases (staghorn calculi). The stones were single in 28% of cases and multiple in 72%. The principal sites were the pelvis (43%) and lower calix (34%).

Treatment

The choice of procedure was determined principally by stone size (Table 1). ESWL was selected for the treatment of small (< 20 mm) non-obstructive intra-renal stones. PCNL was chosen if the stones exceeded 20 mm or if ESWL failed.

For ureteric stones or symptomatic "Steinstrasse", retrograde ureteroscopy was performed. Open surgery was not indicated but in 1 case percutaneous catheter dissolution was used in a residual stone after PCNL.

PCNL consisted of a 1-stage procedure performed under epidural or general anaesthesia (Gelet *et al.*, 1985). The resistance of cystine stones to ultrasound or electrohydraulic devices may lead to mechanical rupture of the collecting system.

Twelve patients were treated by PCNL (26 endoscopic procedures were performed in 19 hospitalisations); 10 patients required complementary ESWL for residual stones inaccessible to PCNL.

Table 1 Treatment of Stones (single or multiple)

	< 10 mm	10–20 mm	20–30 mm	> 30 mm	Total
ESWL	7/18	2/10	0/1	0	9/29
PCNL	0/2	1/3	3/5	1/2	5/12
PCNL+ESWL	1/4	5/6	4/8	1/2	11/20
Total	8/24	8/19	7/14	2/4	24/61

ESWL: Extracorporeal shock wave lithotripsy PCNL: Percutaneous nephrolithotomy

Only 1 percutaneous tract was required in the majority of cases, but 1 patients required 2. In 1 case we attempted to dissolve a residual stone by means of sodium bicarbonate administered through a percutaneous catheter for 13 days.

ESWL was performed using a spark-gap system with an ellipsoidal reflector. The maximum number of shock waves/patient was 2500. Depending on the radio-density of the calculi, a lithotripter with X-ray, localisation system (HM3-Dornier) or ultrasonic system (Sonolith 2000-Technomed I) was employed. ESWL was used alone in 18 cases (2.2 procedures/patient) and in association with PCNL in 7 patients (10 hospitalisations, 2.3 procedures/patient).

Uteroscopy was performed in 1 patient for a large stone impacted in the ureter; the stone was pushed back into the kidney and then treated by PCNL.

All 15 patients received post-operative medical treatment consisting of high fluid intake and urine alkalinisation; in 6 cases this was combined with alpha-mercapto-propionyl-glycine but an adverse reaction occurred in 4 patients and it was discontinued.

Results

The overall stone-free rate was 45% (Table 2).

Analysis according to the method of treatment

ESWL was employed in 18 cases; 7 patients (39%) became stone-free. The mean hospital stay was 5 days and there were no complications.

The percutaneous approach was used alone in 9 patients, 5 of whom (55%) became stone-free; 2.2 procedures were performed per patient. PCNL in association with ESWL was employed in 10 patients, of whom 5 were stone-free (50%). The mean hospital stay was 16 days (Fig. 1A, B). Complications were observed in 3 patients with large kidney stones: 1 pelvic perforation was simply treated by drainage, 1 haemorrhage required transfusion and 1 urosepsis was cured by antibiotic therapy.

Analysis according to location and stone size

For pelvic stones (single or multiple) (Table 3), ESWL alone gave good results and 6/11 patients (55%) with stones < 20 mm became stone-free. PCNL alone gave the best results for stones between 20 and 30 mm (3/4 patients became stone-free) (Fig. 1C, D). For lower calix stones (single or multiple) (Table 4), when ESWL was performed

Table 2 Details of Patients and Treatment

Patient no.	Sex	Age (years)	Stone size (mm)	Treatment	Residual stones	Recurrent stones	Treatment	Residual stones, recurrence	Complementary treatment	Plasma creatinine ($\mu\text{mol/l}$)	Follow-up (months)
1	M	32	48 × 25	PCNL	—	+	ESWL (F) ⇒ PCNL	-/-	—	90	21
2	F	24	47 × 27	PCNL + (I)	+	—	ESWL	+/-	ESWL	76	12
3	M	31	26 × 20	PCNL	—	+	ESWL	-/+	ESWL/PCNL +	87	36
4	M	30	29 × 15 + 7 × 7	PCNL + 2 ESWL	—	+	3 ESWL	-/+	ESWL	174	40
5	M	36	40 × 75	2 PCNL + (U) + 2 ESWL	+	—	—	-/-	PCNL + ESWL	101	3
6	M	46	27 × 22 + 9 × 12	PCNL	+	+	ESWL	-/+	2 ESWL	95	74
7	M	48	26 × 23 + 30 × 11	PCNL + 2 ESWL	—	—	—	-/-	—	102-165	24
8	M	45	25 × 10 + 6 × 12	PCNL + ESWL	+	+	ESWL (F)	-/+	(U)/ESWL(F) ⇒ PCNL	107	36 (D)
9	M	17	23 × 30	PCNL	—	+	ESWL (F) ⇒ PCNL	-/+	—	77	10
10	M	35	18 × 15	ESWL	+	+	PCNL	+/-	PCNL	120	36
11	M	56	21 × 12 + 7 × 4	ESWL	—	+	ESWL	+/-	—	55	36
12	F	36	Complete staghorn	PCNL + ESWL	+	+	ESWL (F)	+/-	PCNL + ESWL	120	24
13	F	25	15 × 20 + 12 × 5	U (P)	+	+	PCNL + 2 ESWL	-/-	—	65.9	12
14	M	44	15 × 12	2 ESWL (F)	+	—	PCNL (waiting)	-/-	—	132	2
15	F	42	10 × 8 + 6 × 6	ESWL	+	—	—	—	—	113	12

PCNL: Percutaneous nephrolithotomy. ESWL: Extracorporeal shock wave lithotripsy. (I): Irrigation. (U): Ureteroscopy. (D): Dead. (P): Pregnancy. (F): Failure.

Table 3 Pelvic Stones (single or multiple)

	< 10 mm	10–20 mm	20–30 mm	> 30 mm
ESWL	4/6	2/5	0/1	0
PCNL	0/1	0/1	3/4	0
PCNL + ESWL	0	2/2	0	1/1

Table 4 Lower Calix Stones (single or multiple)

	< 10 mm	10–20 mm	20–30 mm	> 30 mm
ESWL	1/5	0/4	0	0
PCNL	0	1/1	0	0
PCNL + ESWL	0/1	0	0	0

alone only 1/9 patients (stones <20 mm) became stone-free.

When stones were multiple (27 cases, 3 staghorn) (Table 5), the results of ESWL were poor even for small stones: only a 1/5 success rate for stones <10 mm was observed.

When PCNL was used in association with ESWL, the stone-free rate was 3/4 for stones between 10 and 20 mm and 4/8 for stones between 20 and 30 mm. In the case of staghorn calculi, the stone-free rate was 1/3.

Recurrences

During a 5-year period, 23 recurrences in 11 patients were treated. The recurrence rate per patient and per year was 0.42 (Fig. 1E, F); 20 of the 23 patients with recurrences were on medical treatment and in 13 cases the recurrences were on a retained fragment (either new stone formation or increase in size of a residual fragment). In 10 cases the recurrence was observed in a stone-free patient.

Table 5 Multiple Stones with Multiple Locations

	< 10 mm	10–20 mm	20–30 mm	> 30 mm
ESWL	1/5	0/1	0	0
PCNL	0/1	0/1	0/1	1/2
PCNL + ESWL	1/3	3/4	4/8	partial staghorn 0/1 complete staghorn

Discussion

In the present series only 17/38 patients (45%) became stone-free. This is lower than the rate obtained with non-cystine stones of matched size using the same kind of treatment. Similar results were described by Segura *et al.* (1985) and Knoll *et al.* (1988). Daudon and Reveillaud (1985) described 2 different types of cystine crystal: cystine A and cystine B. Cystine B stones may respond well to ESWL but cystine A stones are very resistant.

PCNL is usually more difficult in the case of cystine stones because of their hardness and multiple locations within the kidney (27/61 in this series) and because the use of the ultrasound probe and electrohydraulic shock waves might damage the excretory tract. If ureteroscopy is decided upon, laser lithotripsy (pulsed dye laser 504 nm) can be inefficient because cystine calculi do not absorb the 504 nm wavelength (Bhatta *et al.*, 1989a and b). *In situ* dissolution of cystine stones can be attempted using percutaneous nephrostomy for antegrade irrigation or by retrograde irrigation through a ureteric catheter. A solution containing N-acetylcysteine plus bicarbonate or Trometamol (Tromethamine-E) can be used. Dredtler *et al.* (1984) showed that the solution with Trometamol was more effective than the combination of N-acetylcysteine and bicarbonate.

As demonstrated by Schmeller *et al.* (1984), dissolution is more efficient after ESWL because of the increased surface contact of fragments. Results obtained by ESWL in cystine stones are not good, but this procedure has no early post-operative morbidity. However, repeated treatment in patients with frequent stone recurrence may produce adverse effects (Lingeman and Kulb, 1987; Montgomery *et al.*, 1989) that are not clearly defined.

We believe that the endourological procedures or ESWL or both should be considered for cystine stones rather than open surgery because the need for nephrectomy has been shown by Daudon and Reveillaud (1989) to increase after each open operation (36/195 cases, 18% nephrectomies in a multi-centre study).

The high recurrence rate and the low stone-free rate obtained after PCNL or ESWL emphasise the importance of medical management. Successful management of cystine stones is based on 3 points: decreasing cystine concentration in urine (increasing fluid intake, diuretics); increasing urinary solubility of cystine by means of alkalisating agents; decreasing cystine excretion by means of a low methionine diet or by transformation into more

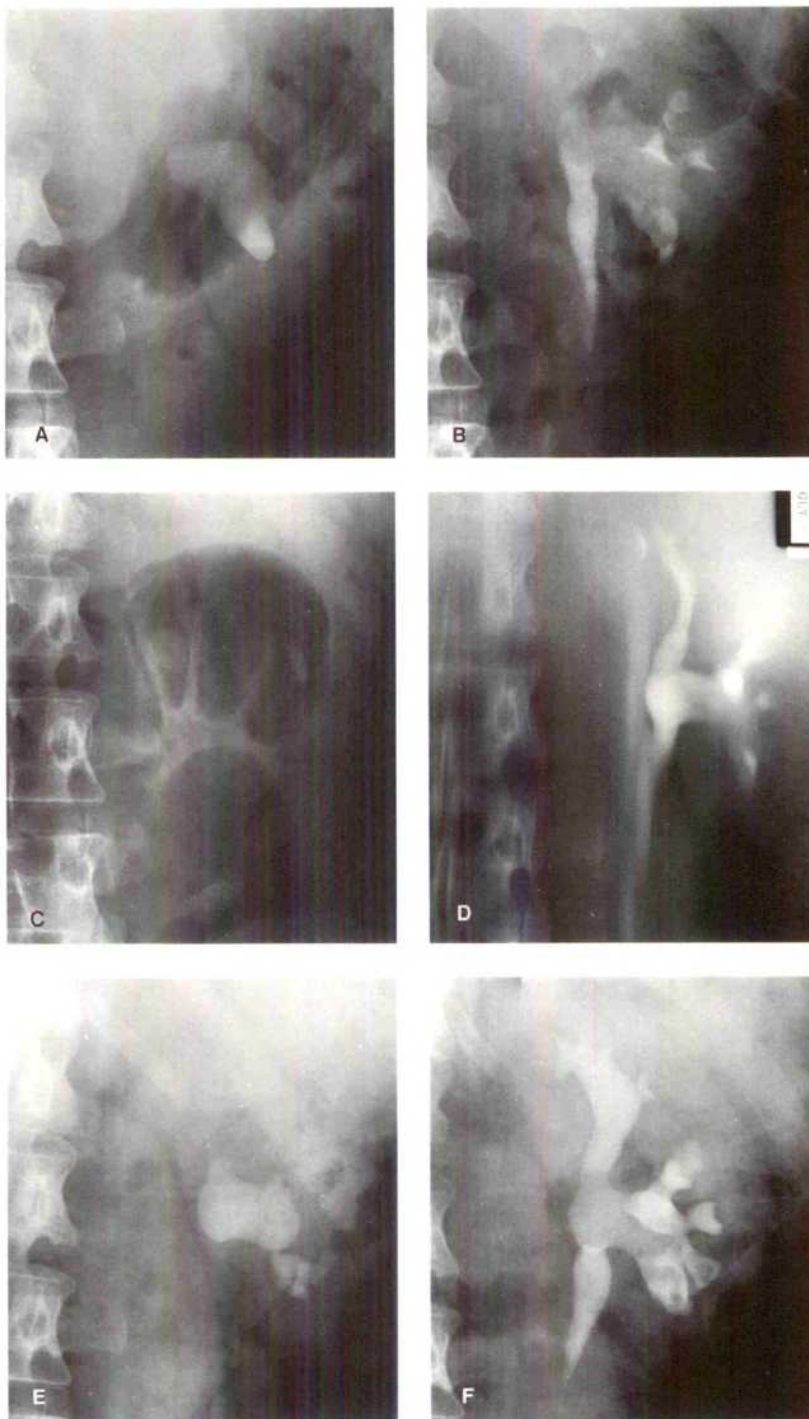


Fig. (A, B) Pelvicalyceal stone before PCNL and ESWL. (C, D) After treatment. (E, F) IVU and plain X-ray 20 months later, showing recurrence.

soluble compounds (D-penicillamine, N-acetyl-D-penicillamine, acetyl-cysteine, alpha-methyl-propionyl-glycine).

In spite of medical treatment the number of recurrences is high. The failure to control cystine nephrolithiasis is sometimes aggravated by poor patient compliance (Thomas *et al.*, 1983) and a coexisting metabolic abnormality such as hyperparathyroidism, hypercalciuria or hyperuricosuria.

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The Effect of Diclofenac Sodium on Urinary Concentration of Calcium, Uric Acid and Glycosaminoglycans in Traumatic Paraplegics

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Summary—Non-steroidal anti-inflammatory drugs (NSAID) have been shown to decrease calcium excretion in the experimental animal, in human volunteers and in calcium stone formers. Paraplegics tend to be hypercalciuric during the first 2 years after their injury and this is said to be a predisposing factor for stone formation in these patients. The effect of the NSAID diclofenac sodium was studied in 12 traumatic paraplegics who had sustained their injury 1 to 6 months previously; 24-h urine samples collected before and 2 weeks and 4 weeks after oral diclofenac sodium 50 mg tds were analysed for calcium, uric acid, glycosaminoglycans (GAGs) and volume. There were no significant changes in urinary volume, uric acid and GAGs excretion. However, urinary calcium concentration and 24-h calcium excretion decreased significantly following 2 weeks' and 4 weeks' treatment with diclofenac sodium.

The prevention of urological complications is a prime objective in the successful rehabilitation of patients with spinal cord injury. Urolithiasis is a well documented complication in traumatic paraplegics. Comarr (1955) reported an incidence of 6.8% for renal calculi and 28% for bladder calculi in adult paraplegics. Tori and Kewalramani (1979) observed that 28% of children with a spinal cord injury developed renal tract stones and most of these (86%) formed during the first year following the injury. One of the predisposing factors for stone formation in these patients is hypercalciuria. Paraplegics are known to have elevated urinary calcium excretion during the first 2 years after their injury (Burr, 1978). The hypercalciuria begins about 10 days after paralysis, reaches a maximum at 10 weeks and persists for at least 6 months (Tori and Kewalramani, 1979). The peak incidence of stone formation occurred between 1½ to 3 years after the spinal cord injury and has been related to the period of hypercalciuria, triggered perhaps by an episode of dehydration or infection with a urease-producing

organism (Freeman, 1949; Guttman and Frankel, 1969; Burr and Nuseibeh, 1985). Eight of 10 patients with bladder calculi had hypercalciuria with positive urine cultures and the hypercalciuria was said to enhance stone formation due to infection with urea-splitting organisms (Tori and Kewalramani, 1979). Thus it is imperative to reduce urinary calcium excretion and concentration in these patients.

The prostaglandin synthetase inhibitor, indomethacin, was found to reduce urinary calcium excretion and calcium concentration in both experimental animals and in hypercalciuric stone formers (Buck *et al.*, 1983). More recently, diclofenac sodium has been used to good effect in the treatment of frequently relapsing calcium stone formers (Brundig and Börner, 1987). We therefore investigated the effect of diclofenac sodium therapy on the concentration and excretion of urinary calcium, uric acid and glycosaminoglycans in a group of traumatic paraplegics.

Patients and Methods

Twelve traumatic paraplegic patients were included in the study. Their spinal cord injuries had been

sustained 1 to 6 months earlier. All were practising clean intermittent self-catheterisation. The urine was cultured and any urinary infections were treated prior to entry into the study. X-ray of the kidneys, ureters and bladder showed no evidence of urinary tract calculi in any patient and all had normal values of serum creatinine and calcium. A 24-h urine sample was collected (Sample 1) for base-line estimation of creatinine, calcium, uric acid and GAGs concentration and excretion. Diclofenac sodium was then prescribed in a dose of 50 mg 3 times a day for 4 weeks; 24-h urine samples were collected at 2 weeks (Sample 2) and at 4 weeks (Sample 3). Care was taken to ensure that no drug therapy was administered during the study period and the patients maintained their usual diet and fluid intake. The total volume of each 24-h urine sample was noted and an aliquot was preserved with a few crystals of thymol. Urinary calcium was determined by the method of Trinder (1960), uric acid by the method of Henry (1961), creatinine as described by Natelson (1963) and GAGs were colorimetrically determined in terms of glucuronic acid by the method of Hesse *et al.* (1986). The urinary concentration and excretion of calcium, uric acid, creatinine and GAGs is given as SI units. The significance of the changes in the urinary concentration of these substances after diclofenac sodium therapy was determined by Student's *t* test for paired samples. The relationship between 24-h urinary excretion of uric acid and GAGs was determined by correlation coefficient.

Results

There were 10 male and 2 female patients in this study and their ages ranged from 21 to 48 years (mean 30.9 ± 7.22). No adverse effects from diclofenac sodium therapy were noted. The results of the urine biochemistry prior to treatment and 2 weeks and 4 weeks following diclofenac sodium administration are shown in the Table. There was no significant change in the 24-h urinary volume after diclofenac sodium and no significant difference in the urinary concentration of creatinine, uric acid and GAGs after 2 and 4 weeks of treatment. The 24-h urinary excretion of calcium decreased from 4.58 ± 1.54 mmol/24 h to 3.35 ± 1.49 mmol/24 h after 2 weeks ($P < 0.01$) and to 3.22 ± 0.66 mmol/24 h ($P < 0.01$) after 4 weeks of treatment with diclofenac sodium.

The urinary concentration of calcium decreased from 4.4 ± 2 mmol/L to 3.32 ± 1.44 mmol/L at 2 weeks ($P < 0.02$) and to 3.32 ± 2.6 mmol/L at 4

weeks ($P < 0.05$). There was no correlation between the urinary uric acid and GAGs concentration in the three 24-h urine samples. There was no significant difference in the urinary concentration of calcium between sample 2 and sample 3.

Discussion

The non-steroidal anti-inflammatory agent, indomethacin, was shown significantly to reduce urinary calcium excretion in normal volunteers and in hypercalciuric stone formers (Buck *et al.*, 1981, 1983). The present study has shown that diclofenac sodium decreases both calcium concentration and excretion in traumatic paraplegics and the drug produced no significant adverse effects. Renal prostaglandin activity appears to be an important factor in the mechanism of calciuria in stone formers. Prostaglandins have been shown to influence the tubular transport of calcium while NSAIDs appear to inhibit calcium binding by cell membranes (Northover, 1973; Buck *et al.*, 1983). The inhibition of prostaglandin-mediated renal 1α hydroxylase activity for the synthesis of $1,25(\text{OH})_2\text{D}_3$ could be another mechanism for the reduction in urinary calcium excretion with diclofenac sodium (Wark *et al.*, 1981).

The incidence of renal tract stone formation in traumatic paraplegics has varied between 20 and 68% (Guttmann, 1973). In a study of 351 paraplegics from World War II a stone incidence of 22% was reported (Guttmann, 1973). However, in 476 patients treated with intermittent self-catheterisation the incidence was only 1.7% (Guttmann and Frankel, 1969). The increased risk of stone formation in paraplegics is far from resolved, especially in developing countries where the medical and nursing care of paraplegics leaves much to be desired. In addition to the control of infection and eradication of urinary stasis, a reduction in the excretion and concentration of calcium would help to reduce the risk of stone formation. Prostaglandin synthetase inhibition with NSAIDs presents a new strategy in the treatment of calcium urolithiasis (Brundig and Börner, 1987). There is a choice of a very wide range of NSAIDs at the present time, but diclofenac sodium appears to have the lowest risk of side effects and interactions. The twisting of the 2 aromatic rings towards one another is regarded as its most important structural parameter. Special importance for drug-receptor interaction is attributed to the specific steric configuration. Long-term treatment is not followed by cumulation in the serum, and kidney function need not be a consid-

Table Urinary Concentration and Excretion of Lithogenic Substances and Inhibitor before and after Therapy with Diclofenac Sodium (50 mg tds)

Parameter	Before therapy	After 2 weeks of therapy	After 4 weeks of therapy
24-h urine volume (ml)	1188 ± 53	1208 ± 65	1425 ± 76
Creatinine (c)	7.04 ± 2.48	6.63 ± 2.04	7.43 ± 2.21
(e)	8.36 ± 2.94	8.01 ± 2.46	10.58 ± 3.14
Calcium (c)	4.37 ± 2.08	3.32 ± 1.44*	3.32 ± 2.67†
(e)	4.58 ± 1.54	3.35 ± 1.49‡	3.22 ± 0.66‡
Uric acid (c)	1.82 ± 0.99	2.11 ± 0.81	1.89 ± 1.15
(e)	2.16 ± 1.17	2.55 ± 0.97	2.69 ± 1.64
GAGs (c)	0.07 ± 0.077	0.06 ± 0.048	0.07 ± 0.05
(e)	0.083 ± 0.091	0.07 ± 0.057	0.09 ± 0.07

c = concentration (mmol/L)

e = excretion (mmol/24 h)

Values are expressed as mean ± S.D. * $P < 0.02$, † $P < 0.05$, ‡ $P < 0.01$.

eration for repeated dosage as the drug is rapidly eliminated (Brundig and Börner, 1987).

Thus diclofenac sodium holds promise in decreasing the occurrence of urolithiasis in spinal cord injury patients by lowering the urinary calcium concentration and 24-h urinary excretion of calcium. However, its clinical potential in the prophylaxis of nephrolithiasis in traumatic paraplegics needs to be evaluated by longitudinal clinical studies.

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Cystometric, Physiological and Morphological Studies after Relief of Bladder Outflow Obstruction in the Pig

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Summary—Experimental bladder outflow obstruction was relieved in 18 pigs between 2 and 15 months after the creation of partial urethral obstruction. Cystometric, physiological and morphological studies were performed 2 to 6 months after relief of the obstruction. An increase in average voiding flow rates from 2.8 ± 1.0 ml/s to 6.8 ± 1.2 ml/s was recorded in the Landrace pigs and from 2.2 ± 0.9 ml/s to 7.4 ± 1.4 ml/s in the Göttingen mini-pigs. There was a concomitant decrease in the voiding detrusor pressures from 52 ± 11 cm H₂O to 32 ± 8 cm H₂O and from 78 ± 12 cm H₂O to 33 ± 6 cm H₂O respectively. A return towards control values of the physiological responses to exogenously applied agonists (acetylcholine and potassium) and to electrical field stimulation was observed. There was an increase in neuronal innervation in the morphological studies which was more marked in the animals with a shorter period of obstruction. The implications for patient care are discussed.

It is well recognised that the majority of patients undergoing prostatectomy for bladder outflow obstruction enjoy a good symptomatic success rate (50–80%) and that many of those patients with detrusor instability secondary to bladder outflow obstruction revert to having stable bladders after prostatectomy (Abrams *et al.*, 1979; Andersen, 1982; Speakman *et al.*, 1987b). Little is known, however, about the factors that affect the chances of a good result after surgery.

Using the pig as an animal model of partial bladder outflow obstruction, we have previously reported the cystometric, physiological and histological changes which occur in the bladder as a consequence of outflow obstruction (Speakman *et al.*, 1987a; Dixon *et al.*, 1989). Elevated voiding pressures, detrusor instability, muscle hypertrophy and a decrease in autonomic innervation were all observed, thus mimicking the changes seen in human subjects with prostatic hypertrophy (Gilpin *et al.*, 1985; Gosling *et al.*, 1986).

Several authors have studied the effects of

variable periods of obstruction in different animal species, on the recovery of these parameters. Acute overdistension of rat and rabbit bladders for a few hours has been shown to lead to reversible degeneration of the intrinsic nerves of the detrusor, but with no changes in the smooth muscle cells themselves (Dunn, 1975; Sehn, 1979). Smooth muscle cell hypertrophy, hyperplasia and collagen infiltration occurred in the rabbit bladder in response to outflow obstruction and, upon relief of the obstruction, both the enlarged cell sizes and the cell numbers regressed to near normal values over periods of up to 4 months. (Brent and Stephens, 1975; Atta and Elbadawi, 1985). Levin *et al.* (1986) showed a 9-fold increase in detrusor mass, a 50% reduction in contractile force to bethanechol and a 75% decrease in the ability to expel saline in the rabbit bladder after partial bladder outflow obstruction. Two weeks after relief of the obstruction all of these parameters had returned towards normal values. Urodynamic studies of bladder outflow obstruction in the pig (Jorgensen *et al.*, 1983) demonstrated an incidence of detrusor instability similar to that which occurs in the human subject

with prostatic enlargement (6 of 7 obstructed pigs becoming unstable). They also showed reversal of the unstable cystometrograms to normal after relief of the partial bladder outflow obstruction in all of the animals studied. Simultaneous studies have confirmed these results and also showed a return towards control values of voiding detrusor pressures and flow rates (Sibley, 1985). A return towards control values was also reported for the *in vitro* responses to exogenously applied acetylcholine and potassium, after relief of experimental obstruction in the pig (Sibley, 1987), but no improvement was seen in the responses to intramural nerve stimulation. Short-lasting obstruction therefore results in functional and morphological changes that are reversible following relief of the obstruction. It is not known, however, whether more prolonged periods of obstruction, or shorter periods of more severe obstruction, lead to irreversible changes in the smooth muscle physiology and morphology of the detrusor.

We therefore report the extension of our previous studies to determine the effect on bladder structure and function of the relief of experimental obstruction.

Materials and Methods

Animals. Nine (of 18) Landrace pigs and 6 (of 12) Göttingen mini-pigs that had been investigated in a study of bladder outflow obstruction (Speakman *et al.*, 1987a) were reassessed after relief of their

partial urethral outflow obstruction. The silver rings (diameter 5–8 mm) were removed after periods of obstruction ranging from 3 to 15 months and these animals underwent follow-up urodynamic studies before being re-biopsied from the anterior wall of the dome of the bladder 2 to 6 months after relief of the obstruction (Table).

Surgical procedures. All operative procedures were performed under general anaesthesia with 1–2% halothane and nitrous oxide/oxygen (2:1). The rings were easily removed, there being little surrounding fibrous tissue. The proximal urethra was dilated to 18 F, via a cystotomy, without difficulty. In 2 animals a stenosis was found to have developed by the time of the subsequent biopsy after 3 and 6 months respectively.

Details of the cystometric techniques and the techniques for preparation of the tissue strips for both the physiological organ bath studies and the light and electron microscopic studies have been previously described (Gilpin *et al.*, 1985; Gosling *et al.*, 1986; Speakman *et al.*, 1987a).

Physiological comparison of the obstructed and post-relief tissues were performed by constructing and comparing the control, obstructed and post-relief dose response curves to acetylcholine and potassium, and the frequency response curves to nerve stimulation. Morphological studies produced data for the neuronal density of acetylcholinesterase-positive nerves, smooth muscle cell size and collagen deposition (light microscopy) as well as

Table Duration and Severity of Obstruction and Cystometric Results during and after Relief of Obstruction

Pig no.	Ring diameter (mm)	Duration of obstruction (months)	Urodynamics (obstructed)	Urodynamics and time after relief (months)	
Landrace pig data					
6	6	3	Stable	Stable	3
7	6	3	Unstable	Stable	3
9	7	3	Unstable	Stable	5
12	7	6	Unstable	Stable	4
13	7	9	Stable	Stable	3
14	7	12	Unstable	Unstable	6
16	8	6	Unstable	Stable	6
17	8	12	Unstable	Unstable	6
18	8	15	Stable	Stable	2
Mini-pig data					
5	5	9	Unstable	Unstable	6
7	5	3	Stable	Stable	3
9	6	3	Unstable	Stable	3
10	6	2	Stable	Stable	3
11	6	2	Unstable	Stable	6
12	6	3	Unstable	Stable	6

providing data on muscle cell structure and total nerve profiles (electron microscopy).

Statistical analysis was performed by comparing comparable points on the dose response curves and the differences in the neuronal densities, using Student's *t* test.

Results

Cystometric results. At the time of removal of the silver rings, 6 of the 9 Landrace pigs and 4 of the 6 mini-pigs had evidence of detrusor instability with phasic rises in detrusor pressure during filling (>15 cm H₂O) that did not result in voiding.

The Table correlates the duration of obstruction and the time after relief of the obstruction with the cystometric results in the individual pigs. The mean detrusor voiding pressure for the 9 Landrace pigs was 52 ± 11 cm H₂O (mean $\pm$ SD) immediately before removal of the silver rings and 32 ± 8 cm H₂O at the time of the final biopsy. There was a concomitant increase in their average voiding flow rates during this period from 2.8 ± 1.0 ml/s (mean $\pm$ SD) to 6.8 ± 1.2 ml/s. The corresponding mini-pig data revealed a drop in voiding detrusor pressure from 78 ± 12 cm H₂O to 33 ± 6 cm H₂O, with an improvement in flow from 2.2 ± 0.9 ml/s to 7.4 ± 1.4 ml/s. At the end of the study 2 of the Landrace pigs and 1 of the Göttingen mini-pigs remained unstable.

Physiological results. The acetylcholine and potassium dose response curves and the frequency response curves to intramural nerve stimulation showed a return towards the values of the control animals (Figs 1, 2 and 3). The ED₅₀ of obstructed animals to acetylcholine was 2×10^{-6} M and that of the animals after relief of the obstruction was 6×10^{-6} M (control values = 5.5×10^{-6} M). The frequency of stimulation required to produce 50% maximal response in the obstructed pigs was 12 Hz and after relief of the obstruction this was 10 Hz (control value = 7 Hz). The relevant data for potassium were 30 mM for the obstructed tissue and 48 mM for the post-relief tissue (control value = 53 mM).

Morphological results. Morphological studies have shown a moderate reinnervation of the tissues and an improvement in the morphological architecture, with a return to normal appearance in the majority of muscle cells, in many of the specimens. Figures 4 and 5 demonstrate the neuronal densities in those Landrace pigs and mini-pigs in which sequential

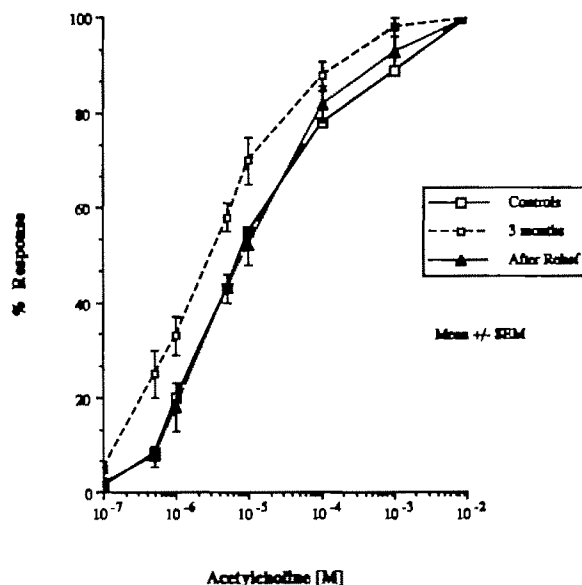


Fig. 1 Acetylcholine dose response curves in Landrace pigs: control, obstructed and post-relief pigs. Responses to a 20-s application of increasing concentrations of acetylcholine ($P < 0.05$ at all points less than 5×10^{-5} M).

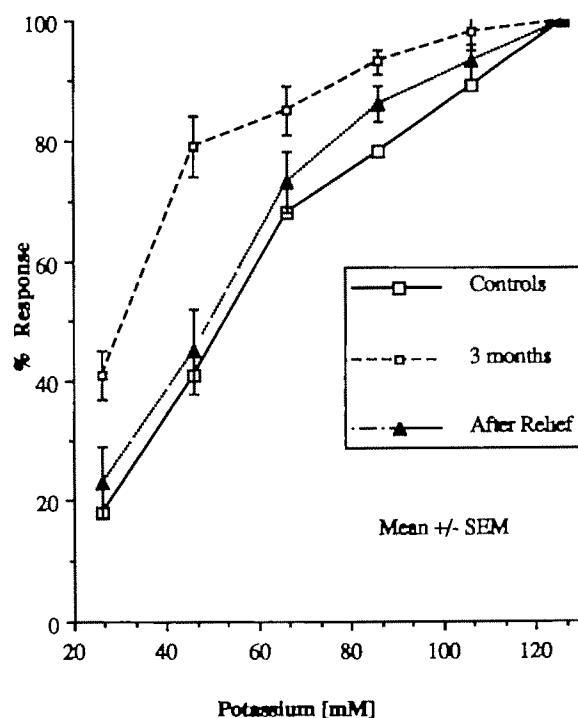


Fig. 2 Potassium dose response curves in Landrace pigs: control, obstructed and post-relief pigs. Responses to a 4-min application of increasing concentrations of potassium. ($P < 0.05$ at all points less than 86 mM).

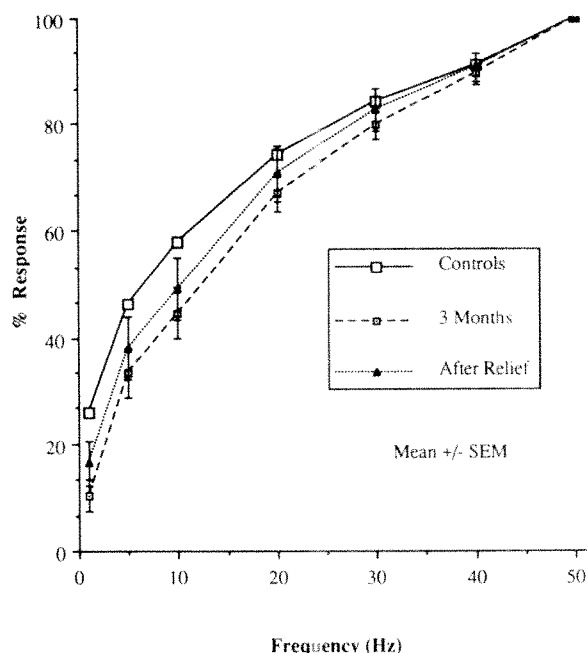


Fig. 3 Frequency response curves in Landrace pigs: control, obstructed and post-relief pigs. Responses to intramural nerve stimulation with 50 volts, 0.05 ms pulse duration and 5-s trains.

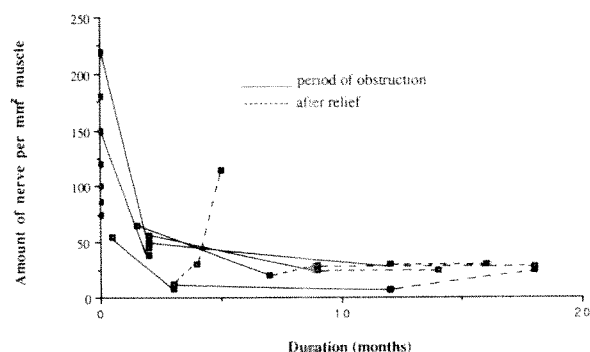


Fig. 4 Landrace pig data: amount of acetylcholinesterase-positive nerve/mm² of detrusor muscle (light microscopy) showing control, obstructed and post-relief of obstruction data.

morphological studies were available. There was only a moderate increase in the neuronal innervation in the Landrace pigs (20–30%) and only 1 animal showed a return to control values. The density of innervation in the mini-pigs returned to control values.

Discussion

It has been shown that relief of obstruction resulted in a significant reduction in the voiding detrusor

pressure and a concomitant increase in flow rates, together with a reduction in the number of animals with overactive detrusor function (detrusor instability) (Abrams *et al.*, 1989). These unstable contractions were always phasic, although 2 animals also had a progressive rise in pressure during filling > 15 cm H₂O: low compliance (nos 12 and 14).

Because of the variation in ring sizes of the animals used for the post-relief studies and the varying periods of obstruction that they had undergone, it was difficult to ascertain the relationship between ring size (taken to represent the severity of obstruction), the duration of obstruction and the persistence of instability. Animals with all sizes of rings (5–8 mm) had developed instability and although the mini-pig with unstable contractions persisting after relief of the obstruction belonged to the most severely obstructed group (5 mm), both of the Landrace pigs with severe obstruction (6 mm) had stable bladders 3 months after removal of the silver ring. It is perhaps significant that the mini-pig with the longest duration of obstruction (no. 5; 9 months) and the 2 unstable Landrace pigs with the longest periods of obstruction (no. 14; 12 months and no. 17; 12 months) were all still unstable 6 months after relief of obstruction. However, the Landrace pig with the longest period of obstruction (no. 18; 15 months) remained stable throughout the study. There is therefore no linear correlation with the duration of obstruction and either the development of instability or its persistence after relief of the obstruction.

The organ bath studies have shown a shift towards control values of the responses to acetylcholine, potassium and intramural nerve stimulation, with a change in the corresponding ED₅₀s. These data would indicate an improvement in the

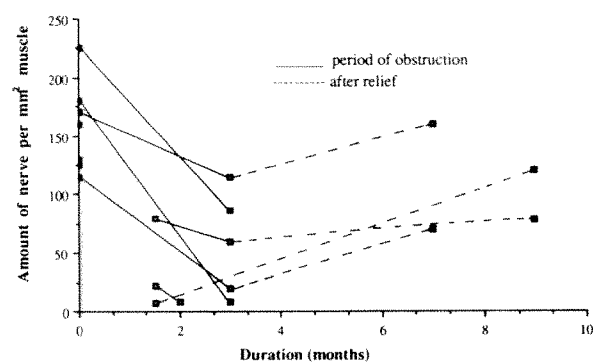


Fig. 5 Mini-pig data: amount of acetylcholinesterase-positive nerve/mm² of detrusor muscle (light microscopy), showing control, obstructed and post-relief of obstruction data.

smooth muscle physiology of the detrusor after relief of the obstruction. No significant difference was noted, however, between the animals that had reverted to stable cystometrograms and those that were still unstable.

The morphological data demonstrated a variable increase in neuronal innervation. The only Landrace pig to have had a short period of obstruction (and sequential biopsies for histological studies) showed a marked increase in neuronal density. The remaining Landrace pigs showed only a moderate reinnervation. The mini-pig biopsies, however, showed a universal significant increase in neuronal density following relief of obstruction. None of these animals had been obstructed for more than 3 months.

Thus it would seem that the degree of reinnervation after relief of obstruction is related to the duration of obstruction. The relationship, however, between the degree of reinnervation and the persistence of instability is less clear. This would again indicate a complex relationship between outflow obstruction and detrusor damage. Clinical studies in patients with outflow symptoms have shown an association between the duration of symptoms and the presence of instability and in turn the increased likelihood of a poor outcome after surgery (Speakman *et al.*, 1987b). These findings, taken with those of the present study, indicate a need to take into account both the duration and severity of obstructive symptoms in formulating patient waiting lists.

More detailed studies of the cellular morphology of these specimens are being undertaken. It is hoped that these may show some link between the smooth muscle changes at a cellular level and the presence or persistence of instability.

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Cytokeratin Shedding in Urine as a Biological Marker for Bladder Cancer: Monoclonal Antibody-Based Evaluation

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Summary—Cytokeratin shedding into urine was measured using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) in 282 individuals. Samples included urine from normal controls, patients with urogenital conditions and bladder cancer patients. A monoclonal antibody prepared against cytokeratins extracted from a hyperkeratotic low grade squamous cell carcinoma (UNME/K1) was used in the assay. The results indicated reasonable levels of sensitivity (83%), specificity (67%) and overall accuracy (70%) in the detection of bladder cancer. The levels of sensitivity in detecting squamous and transitional cell carcinoma patients were 87 and 73% respectively. The low level of specificity was due to a high frequency of false positive results (55%) within the urogenital controls; this suggests that further immunochemical and immunohistopathological analyses of associated urothelial cytokeratins are required.

The diagnosis of bladder cancer usually involves cystoscopic examination and biopsies for histological study and often requires hospitalisation of the patients. Thus a procedure for analysis of urine is needed that is simple, non-invasive and reproducible. Urine cytology is subject to many factors, including tumour grade, collection techniques, experience of the cytotechnologists and other laboratory variables (Frable *et al.*, 1977). Many urinary biological markers have been evaluated, *e.g.* cell surface antigens (Young *et al.*, 1979), carcinoembryonic antigen (Betkerur *et al.*, 1980), urinary immunoglobulins (Kumar *et al.*, 1981), tissue polypeptide antigen (McCabe *et al.*, 1984) and oncogene products (Stock *et al.*, 1987). None of the tumour markers used at present reaches the required standards of high specificity and sensitivity (Birkmayer, 1988). Over the last decade, cytokeratin (which constitutes the intermediate filament system of epithelial cells) (Feitz *et al.*, 1986) has

been considered as another possible marker (Tseng *et al.*, 1982; Woodcock-Michell *et al.*, 1982; Baker *et al.*, 1988).

Basta *et al.* (1988) indicated that cytokeratin shedding in urine can be detected by its immunological reactivity with both polyvalent and commercial monoclonal antibodies (Mab) in a blocking enzyme-linked immunosorbent assay (ELISA). In the present study we have tried to improve specificity and sensitivity using locally prepared Mab in a double sandwich ELISA.

Materials and Methods

Collection and processing of urine specimens

A total of 282 random voided urine samples (excluding those from patients with indwelling urinary catheters) were obtained from 89 healthy individuals, 136 control individuals with urogenital conditions (most with a high possibility of keratinising metaplasia) and 57 patients with urinary bladder carcinoma. The sex distribution, mean age and incidence of schistosomiasis are presented in

Table 1. The tumours were staged histologically according to the UICC (1978) classification and graded according to the recommendations of Mostofi *et al.*, (1973) (Table 2).

Keratin extraction from urine was performed basically according to the method of Winter *et al.* (1980). A 10-ml aliquot of each urine sample was centrifuged at 3500 rpm for 30 min. The pellet was washed with high salt buffer (1.5 M KCl, 2 mM dithioerythrol, 0.5 mM phenylmethylsulphonyl-fluoride, 0.5% Triton X-100, and 10 mM Tris-HCl pH 7.5) under constant spinning for 5 min. It was further centrifuged at 3500 rpm for 30 min and the supernatant discarded.

The pellet was solubilised in 2 ml keratin-dissociation buffer (8 M urea, 50 mM Tris-HCl, pH 9.0) by vigorous spinning for 5 min. The dissociated suspension was centrifuged for 20 min

at 3500 rpm. The clear supernatant was then used as test material.

The specimens were randomly arranged and coded before testing. The protein content of urine extracts was determined by the ultraviolet absorption method with some modification according to Waddell and Hill (1956). The protein concentration of samples was calculated according to Johnstone and Thorpe (1982) using the following equation:

$$\text{Protein concentration (mg/ml)} = (1.55 \times \text{absorbance at 280 nm}) - (0.77 \times \text{absorbance at 260 nm})$$

Anti-keratin antibodies

Two different anti-keratin antibodies were used. One was a polyclonal antibody raised in guinea pigs against soluble keratin extract isolated from human urinary bladder squamous cell carcinoma. The other was a monoclonal antibody (UNME/K1) produced against cytokeratins extracted from a hyperkeratotic low grade squamous cell carcinoma of human urinary bladder (El-Mohamady *et al.*, 1990). The reactivity for both antibodies was confirmed by direct ELISA. By affinity chromatography, UNME/K1 Mab was confirmed to react with the 66, 56 and 48 Kd cytokeratin polypeptides.

Enzyme-linked immunosorbent assay (ELISA)

The double antibody sandwich ELISA technique of Voller *et al.* (1974) was used (with modifications) to detect cytokeratin shedding in urine. Flat-bottom polyvinyl 96-well microtitre plates (Flow Laboratories, Irvine, UK) were coated with 100 µl/well of 10 µg/ml anti-keratin polyclonal antibody diluted in 0.1 M sodium carbonate buffer pH 9.6. The plates were incubated overnight in a humidified atmosphere at room temperature, then washed with 0.01 M phosphate buffered saline (PBS), pH 7.2. Blocking of any free sites remaining on the plates was performed using 5% foetal calf serum (FCS) in carbonate buffer. After washing the plates with PBS containing 0.05% Tween-20, 100 µl of test samples [0.15 mg/ml in Tris-SDS buffer (10 mM Tris-HCl 0.1% SDS, pH 7.6) containing 1% FCS] were added to duplicate microtitre wells and the plates were incubated for 2 h at 37°C. After washing, 100 µl/well of the second antibody (UNME/K1 Mab) diluted 1:15,000 in Tris-HCl buffer (50 mM Tris-HCl pH 9.0) was added and incubated for 2 h at 37°C. Washing was repeated and 100 µl of an optimal dilution (1:1000) of anti-mouse IgG peroxidase conjugated antibody (Sigma Chemical Co., St Louis, USA) was added to each

Table 1 Details of Patients

Status	No. of subjects	Mean age	Sex distribution		Schistosomiasis incidence
			M	F	
Normal controls	89	30	17	72	—
Urogenital controls	136	41	113	23	23
Bilharziasis	19	34	14	5	19
Urinary stones	54	40	46	8	—
Cancer of prostate	4	50	4	—	1
Pregnancy	8	31	—	8	—
Others	37	45	36	1	3
Others with catheter	14	48	13	1	—
Bladder Carcinoma	57	55	40	17	39
Squamous cell	23	47	13	10	23
Transitional cell	30	53	23	7	12
Adenocarcinoma	4	55	3	1	4

Table 2 Histopathological Distribution of Tumours

	Histological grade	No. of patients	Pathological stage			
			P1	P2	P3	P4
Squamous cell carcinoma	G1	16	—	—	16	—
	G2	4	—	—	4	—
	G3	3	1	—	2	—
Transitional cell carcinoma	G1	7	7	—	—	—
	G2	22	8	2	10	2
	G3	1	—	—	1	—
Adenocarcinoma	G1	1	—	1	—	—
	G2	1	—	—	1	—
	G3	2	—	—	2	—

well and incubated for 2 h at 37°C. Following 3 washes, 100 µl of orthophenylene diamine substrate solution (0.034% in citrate-phosphate buffer pH 5.0 (49 ml of 21.0 g/L citric acid and 51 ml of 38.6 g/L Na₂ HPO₄) + 10 µl of 30% H₂O₂) was added to each well and allowed to react for 20 min at room temperature in complete darkness. The enzyme reaction was stopped by addition of 25 µl of 1 N HCl. Absorbance (Ab) was measured at 492 nm using a multichannel photometer (Flow Laboratories).

Mathematical evaluation

Evaluation of data with regard to sensitivity and specificity was performed on the basis of the receiver operating characteristic (ROC) curve according to McNeil *et al.* (1975). When necessary, statistical analysis was done by the χ^2 and Fisher's tests.

Results

Individual samples were exposed to the double antibody sandwich ELISA twice. After the first analysis, 2 highly positive samples were mixed and used as a serially diluted positive control. Intra-assay reproducibility was evaluated by 8 replicate determinations of 4 dilutions of the positive control (Fig. 1). The absorbance value increased proportionally with the increase of the concentration. The highest absorbance value was obtained at the 0.15 mg/ml concentration with a 7.5% variance coefficient. This concentration was used for the application of each sample in the second ELISA run. The assay batch-to-batch variation in the reactivity of the positive control was accepted when it fell within 5% of the mean reading. Inter-assay reproducibility was evaluated by a total of 48 individual determinations of the 4 dilutions of the positive control, tested in duplicates over 6 runs.

Before any evaluation of the assay results, the ROC curve (Fig. 2) was performed using different absorbance values as hypothetical cut-off points. The 0.4 value was chosen as the cut-off point between the positive and negative urinary cytokeratin shedding test. The distribution of individual results of the 89 normal controls, 136 urogenital controls and 57 bladder cancer patients was related to the cut-off point (Fig. 3).

In order to evaluate our assay with regard to the detection of bladder cancer, assay reactivity, sensitivity, specificity and overall accuracy were analysed. For the assay reactivity (Table 3), the level was highest (83%) within the bladder carcinoma

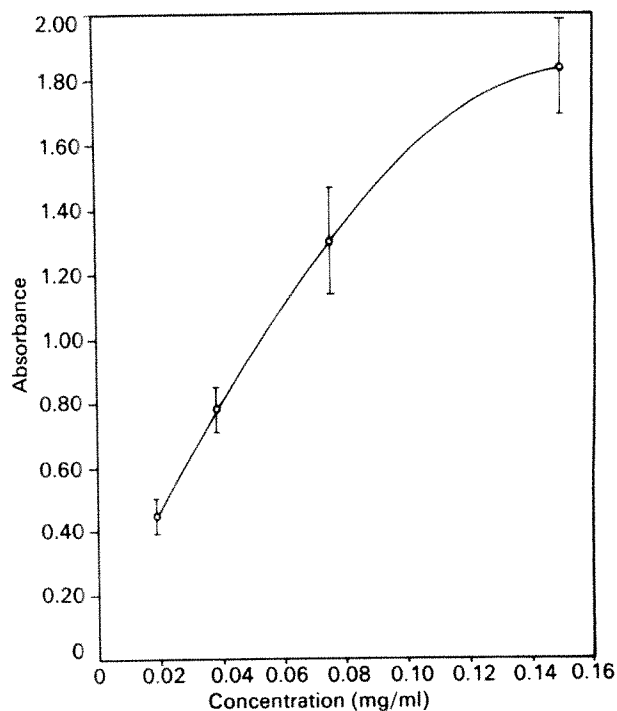


Fig. 1 Standard curve of the serially diluted positive control sample. The concentration is expressed as total protein content. The corresponding absorbance value for each concentration is the mean of 8 replicate readings ($\pm$ SE).

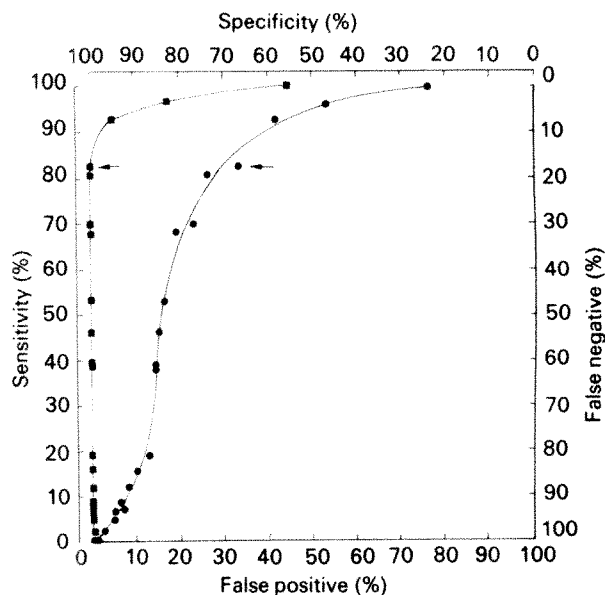


Fig. 2 ROC-analysis of specificity and sensitivity related to cytokeratin shedding in urine at different absorbance values (hypothetical cut-off points). At absolute specificity, derived from the reactivity of normal control specimens (■), the corresponding cut-off point was at 0.4 absorbance value (indicated by arrows). At this value, analysis based on all control specimens (●) was performed.

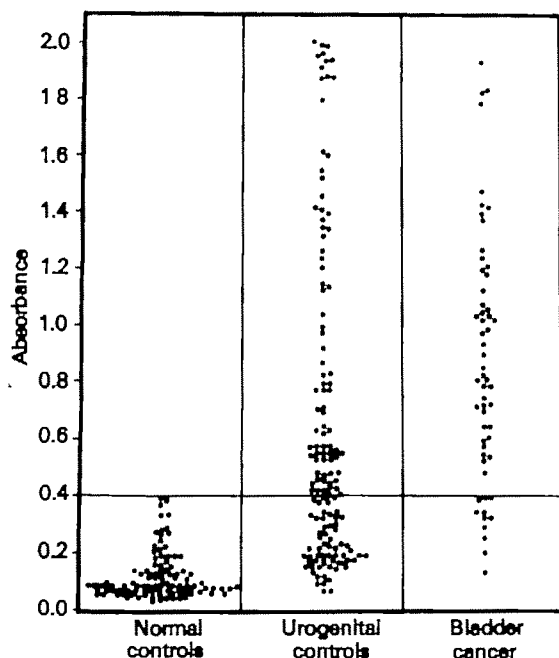


Fig. 3 Cytokeratin individual titres of 282 urine specimens examined by cytokeratin shedding assay. The horizontal line at 0.4 absorbance value indicates the cut-off level for reactivity.

group. On the other hand, a moderate reactivity level of 55% was expressed by samples of the urogenital control group and considered as a false positive. The difference in reactivity of the 3 groups was significant ($P < 0.05$).

Although the false positive reactivity within the subgroups of urogenital controls did not show significant correlation, the potential influence of schistosomiasis on cytokeratin shedding into urine was studied (Table 4). The correlation between cytokeratin shedding and schistosomiasis was not significant ($P > 0.05$).

The assay sensitivity evaluation within bladder carcinoma subgroups (Table 5) indicated a higher

Table 4 Schistosomiasis Related Reactivity within Urogenital Controls

Schistosomiasis	No of patients	Cytokeratin shedding	
		Positive	Negative
Positive	23	10 (31%)	13 (69%)
Negative	113	65 (58%)	48 (42%)

$P > 0.05$

percentage (87%) within the squamous type than within the transitional type (77%). However, this did not reach statistical significance ($P > 0.05$).

Table 6 shows the assay evaluation parameters, i.e. specificity, sensitivity and overall accuracy. The specificity of the assay was defined as the percentage of 89 normal and 136 urogenital controls with a negative urinary cytokeratin test in relation to the total number (225) of these individuals. Specificity was 67%, this is a reflection of 75 false positive results within the urogenital controls. The assay sensitivity in detecting bladder cancer patients was defined as the percentage of 57 individuals with a positive cytokeratin shedding test; this is a reflection of 10 false negative results. The assay was found to be 83% sensitive. In addition, the overall accuracy of the assay (defined as the percentage of correctly identified cases in relation to a total of 282 individuals tested) reached 70%.

Discussion

Non-invasive and rapid diagnostic tests are needed in the assessment of all potential malignancies on the basis of specific tumour markers. Numerous attempts have been made in recent years to identify biological markers of bladder cancer in urine (Liu

Table 3 Assay Reactivity

Test group	No. of patients	Cytokeratin shedding		% positive*
		Positive	Negative	
Normal controls	89	0	89	0
Urogenital controls	136	75	61	55
Bladder carcinoma	57	47	10	83

*Percentage of positive cytokeratin shedding in relation to the number of tested cases.

Table 5 Assay Sensitivity in the Detection of Bladder Carcinoma Subgroups

Test group	No. of patients	Cytokeratin shedding		% positive*
		Positive	Negative	
Squamous cell carcinoma	23	20	3	87
Transitional cell carcinoma	30	23	7	77
Adenocarcinoma	4	4	0	100
Total	57	47	10	83

*Percentage of positive cytokeratin shedding in relation to the total number of bladder cancer cases
 $P > 0.05$

Table 6 Assay Evaluation Parameters

Test group	No. of patients	Cytokeratin shedding		% of evaluation parameter
		True positive	True negative	
Normal and urogenital controls	225	—	150	67 specificity*
Bladder carcinoma	57	47	—	83 sensitivity†
Total	282	47	150	70 overall accuracy‡

$$* \text{Specificity} = \frac{\text{No. of true negative cases}}{\text{No. of control cases}}$$

$$† \text{Sensitivity} = \frac{\text{No. of true positive cases}}{\text{No. of bladder cancer cases}}$$

$$‡ \text{Overall accuracy} = \frac{\text{No. of correctly identified cases}}{\text{total no. of cases tested}}$$

et al., 1987; Guirguis *et al.*, 1988; Malmstrom *et al.*, 1988; Carbin *et al.*, 1989). In a previous report (Basta *et al.*, 1988) we suggested the potential usefulness of cytokeratin as a new and specific urinary marker for bladder cancer patients. The findings of that report led us to produce a Mab with specificity towards cytokeratin polypeptides present in squamous cell carcinoma.

The present study was designed to improve the specificity and sensitivity for detecting bladder malignancy based on cytokeratin shedding into urine as a biological marker. UNME/K1 Mab, prepared against cytokeratins of a hyperkeratotic low grade squamous cell carcinoma, was used in a double sandwich ELISA technique. Sandwich ELISA is thought to be sensitive in antigen assays (Voller *et al.*, 1976). The use of polyclonal specific antisera as a capture antibody would allow binding of antibodies to multiple epitopes. The specificity of the assay remains, however, with the specificity of the Mab. The UNME/K1 Mab was confirmed to react with cytokeratin polypeptides characteristic of squamous cell carcinoma lesions as classified by Moll *et al.* (1982).

At the chosen cut-off point, the assay correctly identified 70% of the total population tested. In relation to the detection of bladder malignancy, the assay can differentiate significantly between patients with bladder cancer and normal individuals. On the other hand, there was no significant differentiation between the carcinoma subgroups.

Cytokeratin shedding was detected in 55% of patients with urogenital conditions other than bladder cancer. Our observations seem to imply that cytokeratin shedding into urine and schistosome infestation were not related.

Although the exact cause of the false positive

results is not clear, they may result from the partial homology of the keratin epitope recognised by the monoclonal antibody with a related epitope. This would not be surprising, given the extensive homology of the entire family of intermediate filaments (Gown and Vogel, 1982). Alternatively, one has to consider the possibility that some neoplasms manifest aberrant synthesis or abnormal post-translational processing of intermediate filaments as a result of the malignant transformation. It is also possible that other unrelated antigens are responsible for the apparent cross-reactivity (Battifora, 1988).

The results of the present study indicate that the sandwich ELISA is more sensitive in detecting bladder cancer than the blocking ELISA of Basta *et al.* (1988). However, the specificity in this sandwich ELISA was 67% compared with 81% in the blocking ELISA (Basta *et al.*, 1988). As a consequence, the overall accuracy fell to 70%. The UNME/K1 Mab used in the sandwich ELISA reflected the same specificity when compared with the results of both anti-keratin antibodies (the polyvalent antibody and EAB-903 Mab) used in the blocking ELISA. Only the use of PKK-2 Mab (Basta *et al.*, 1988) indicated a higher specificity.

Studies of larger number of patients will allow us to address the value of cytokeratin as a tumour marker. Otherwise, the false positives in the urogenital controls render the procedure in its current form unreliable for clinical use. We suggest using 2 monoclonal antibodies or a monoclonal antibody cocktail for the assay. In addition, schistosomal bladder cancer-associated cytokeratins have to be clearly defined and so there is a need for more immunochemical and immunohistopathological studies.

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Adenocarcinoma of the Bladder: Study of 14 Cases and Review of the Literature

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Summary—Fourteen patients with adenocarcinoma of the bladder have been seen over a 14-year period; 6 tumours were of urachal origin and the remaining 8 were primary. All tumours were muscle-infiltrating. The 6 patients with urachal tumours were subjected to surgery; 3 underwent partial cystectomy and 3 radical total cystectomy. All patients who underwent partial cystectomy are alive and free of disease at 60 months, 12 months and 12 months respectively. The other 3 patients who underwent radical cystectomy suffered recurrence and 2 succumbed to their disease within 1 year. All patients with primary adenocarcinoma of the bladder underwent radical cystectomy, 5 of them after planned pre-operative radiotherapy. There were 3 post-operative deaths. One patient died of an unrelated cause 30 months after surgery and 2 died of disseminated disease 8 and 16 months after surgery. One patient developed inguinal lymph node metastases 4 months after surgery and is controlled at 12 months with radiotherapy. Only 1 of the 8 patients with primary adenocarcinoma of the bladder is alive and free of disease at 6 months.

Adenocarcinoma of the bladder is an uncommon neoplasm, with a reported incidence of 0.5 to 2% of urothelial vesical neoplasms. So far only about 200 cases have been reported in the literature, indicating paucity of material for review (Thomas *et al.*, 1971; Jacobo *et al.*, 1977; Jones *et al.*, 1980). Approximately 25 cases of signet ring cell carcinoma have been described, while only about 9 cases of mesonephric adenocarcinoma have been documented so far. Adenocarcinoma can exist in a pure form or as part of a mixed tumour with other epithelial elements such as transitional or squamous or as part of a carcinosarcoma (Schoborg *et al.*, 1980; Smith *et al.*, 1983). It is the most common malignant tumour occurring in an exstrophied bladder (Abeshouse, 1943) and more frequently seen in schistosomiasis-infested bladders (Makar, 1962).

We have reviewed 14 cases of adenocarcinoma of the bladder seen at this centre over a 14-year period.

Patients and Methods

Fourteen patients with adenocarcinoma of the bladder were treated at this hospital between 1976 and 1989. In all cases the initial diagnosis of adenocarcinoma was established following cystoscopic bladder biopsies. Clinical, radiological and pathological investigations were carried out to establish whether the tumours were primary or secondary. In tumours thought to be secondary to invasion from the surrounding organs, a full gastrointestinal and gynaecological evaluation was done to rule out such a possibility. Clinical staging was done by bimanual examination under anaesthesia and was supported in some patients by computed tomography. All patients underwent chest X-rays and isotope bone scans to exclude metastatic disease.

Five of the 6 urachal tumours located in the upper half of the bladder were treated with radiotherapy prior to surgery. Eight patients with primary adenocarcinoma of the bladder were treated with radical cystectomy; 5 with and 3 without pre-operative radiotherapy. After completion of the primary treatment, all patients were

followed up regularly at 3-monthly intervals, with clinical and radiological evaluation at each visit.

Follow-up ranged from 6 to 168 months. The patients were studied with reference to age, sex, symptomatology, pathological findings, tumour stage, mode of primary treatment, local and distant recurrences and survival rates.

Results

Of the 14 cases of adenocarcinoma of the bladder, 6 were urachal in origin and the remaining 8 were primary adenocarcinomas. Eleven of the 14 patients were in the fifth to the seventh decades, the youngest being 30 years old, and the eldest 66. There were 10 males and 4 females. Urachal carcinomas occurred in a younger age group than did primary adenocarcinomas of the bladder and were seen more often in females. Haematuria, with or without bladder irritability, was the commonest symptom, present in 13 of 14 patients, while 1 patient had only symptoms of bladder irritability. All patients had solitary tumours. In 6 patients they were located at the dome and in the remaining 8 they were confined to the lower half of the bladder. A pre-operative diagnosis of primary or urachal adenocarcinoma was established in all cases. Nine patients had poorly differentiated tumours and 5 had well or moderately differentiated tumours.

All 6 urachal tumours were muscle-infiltrating on bimanual examination, 3 of them with deep muscle infiltration, while the remaining 3 showed additional peri-vesical spread. Of these 6 patients, 5 were subjected to pre-operative radiotherapy followed by surgery. Three patients were treated with partial cystectomy and 3 with radical cystectomy. In all cases, the disease was deeply infiltrating, being downstaged in 2. Pelvic lymph node metastasis was not observed in any of these cases. One of the 3 patients who underwent partial cystectomy was alive at 5 years, while the other 2 were alive and free of disease at 1 year. All 3 patients who were treated with radical total cystectomy developed recurrent tumours within 15 months. Two succumbed to their disease (1 with a pelvic recurrence and the other with liver metastasis) within 1 year of surgery, while the third patient had recurrence in the para-aortic nodes 15 months after surgery and was alive with disease at 24 months. Partial cystectomy for urachal carcinoma yielded better survival rates than did radical cystectomy but this was probably related to volume of disease and location of tumour. In the former group, the

tumour volume was comparatively small, making partial cystectomy possible.

All 8 primary non-urachal adenocarcinomas were infiltrating, 5 with deep muscle infiltration and 3 with perivesical spread also. The patients were treated with radical total cystectomy: 5 with pre-operative radiation therapy and 3 without it. Histopathological examination of the cystectomy specimens showed that all patients had deeply infiltrating tumours, with involvement of the prostate in 1 case. Pelvic lymph nodes were metastatic in 3 patients and para-aortic nodes in 1. There were 3 post-operative deaths in this group. In addition, 3 patients died 8, 30 and 36 months after surgery. One patient died of an unrelated cause 30 months following surgery and was completely free of disease at the time of death, and 1 patient died of disseminated disease with skeletal metastasis 8 months after surgery. One patient developed metastasis in the para-aortic nodes and liver 18 months following surgery; he was treated with combination chemotherapy and died 36 months after cystectomy. Another patient developed metastases in the inguinal nodes 4 months after cystectomy, was treated with chemotherapy and was alive and free of the disease at 12 months. The last patient was alive and free of disease 6 months after surgery. There were no adenocarcinomas secondarily involving the bladder.

Discussion

Adenocarcinoma of the bladder can be broadly classified into 3 categories:

- (1) Primary adenocarcinoma of the bladder.
- (2) Urachal carcinoma.
- (3) Metastatic carcinoma or carcinoma infiltrating the bladder from neighbouring sites.

Adenocarcinoma of the bladder occurs more frequently in the fifth to the seventh decades, although occasional cases have been reported in the paediatric population (Raghavaiah, 1980). It is more prevalent in males, with a reported male to female ratio of 2:1 (Mostofi *et al.*, 1955; Thomas *et al.*, 1971; Bennett *et al.*, 1984). The symptoms are usually non-specific and include haematuria, pyuria and lower urinary tract symptoms, although the presence of urinary mucus may suggest the presence of glandular epithelium (Wheeler and Hill, 1954). Although multiple tumours may be seen, adenocarcinomas of the bladder are usually solitary (Mostofi *et al.*, 1955). Adenocarcinomas are seen more commonly in the dome, trigone and bladder neck

than are conventional urothelial tumours, <10% of which are located in the dome (Wheeler and Hill, 1954; Winter and Goodwin, 1959). Compared with urothelial tumours, adenocarcinomas are less inclined to be multifocal or to recur within the bladder mucosa (Anderstrom *et al.*, 1983). These factors were all evident in our patients.

Cystoscopic appearances are seldom diagnostic in themselves but, as a rule, these lesions tend to be more infiltrating than mucosal. Local spread in the bladder wall and outside the adventitia of the bladder is disproportionately large compared with growth within the bladder cavity. If the extent of the tumour on bimanual examination is greater than that seen on cystoscopy, adenocarcinoma should be suspected. Signet ring cell carcinoma may show a peculiar growth characterised by diffuse thickening of the whole bladder wall, in which case it may be very difficult to pinpoint the abnormal area on cystoscopy.

Most of the urachal adenocarcinomas are advanced tumours at the time of diagnosis. Since their location at the vault and their predominantly extramucosal nature keeps them asymptomatic until a late stage, approximately two thirds of tumours are deeply invasive at the time of presentation (Anderstrom *et al.*, 1983). Primary adenocarcinomas of the bladder also present in an advanced stage, irrespective of their site in the bladder, and hence have a poorer prognosis than conventional urothelial tumours. Survival is also related to tumour grade and, the majority being poorly differentiated, survival rates are usually poor. Tumour size is another variable that influences the prognosis (Anderstrom *et al.*, 1983).

The distinction between primary bladder adenocarcinoma and urachal adenocarcinoma is important in deciding on the optimum form of treatment. Primary bladder adenocarcinomas merit radical total cystectomy, as compared with partial cystectomy for urachal carcinomas (Abenzoa *et al.*, 1987). The distinction between the 2 cannot be made on the basis of histology alone but by correlation with tumour site, presence of cystitis glandularis in the surrounding mucosa and, rarely, histochemical studies (Wells and Anderson, 1985). The distinction between primary or urachal adenocarcinomas and secondary adenocarcinomas is difficult at times. A careful search for the primary tumour elsewhere, together with histological and immunohistochemical studies, may be helpful (Alroy, 1981).

Urachal tumours are usually treated with partial cystectomy with excision of the umbilicus. Gill *et al.* (1989) reported a 44% 2-year survival rate in

such cases. Whitehead and Tessler (1971) reported a 25% 5-year survival rate with such a procedure. However, bearing in mind the peculiarly wide and deep infiltration of the muscular layer of the bladder, with an intact mucosa and the high rate of lymph node metastasis, Kakizoe *et al.* (1983) carried out extended radical cystectomies for urachal adenocarcinomas and reported improved survival rates. Inadequate partial excision of the tumour leads to a higher incidence of local recurrences and poorer survival rates while a wide partial cystectomy with histologically negative margins yields survival rates equivalent to those after radical cystectomy.

Abenzoa *et al.* (1987) and Gill *et al.* (1989) have advised frozen-section examination of the cut margins of excised specimens. Adenocarcinomas of the bladder are relatively radioresistant. Chemotherapy has no favourable long-term benefits, though few reports of its efficacy are available, either with the single drug 5-fluorouracil or a multi-drug regimen with ifosofamide, nismustine hydrochloride and dacarbazine (Nevin *et al.*, 1974; Logothetis *et al.*, 1985; Hatch and Fuchs, 1989). These claims, however, are based on results in a small number of patients. We achieved better results with partial cystectomy in patients with urachal carcinoma, while those undergoing radical surgery had a poor outcome mainly because of large-volume infiltrative disease.

Primary adenocarcinomas of the bladder are more common in the lower half of the bladder and hence are less amenable to treatment with conservative surgery. Radical cystectomy is the treatment of choice and many have claimed good results (Jones *et al.*, 1980; Malek *et al.*, 1983; Bennett *et al.*, 1984), while partial cystectomy has uniformly yielded poor results (Jones *et al.*, 1980; Gill *et al.*, 1989). Of the 8 patients in the present series, despite radical surgery, only 2 were alive for 6 months and 12 months when last seen. Since 3 died post-operatively, only 5 patients were available for evaluation; 2 of these had pelvic and liver metastases because of large-volume extensive disease, while the third died without any evidence of disease 30 months after surgery. The 2 patients who are alive have a very short follow-up. Patients with high stage and high grade disease have a very poor survival rate.

It is apparent from the data that primary adenocarcinoma of the bladder is an aggressive tumour. In relation to prognosis, several variables are considered important, the stage of the disease being most significant (Abenzoa *et al.*, 1987) and the others being tumour grade and tumour size.

The site of the tumour *per se* has no bearing on survival (Anderstrom *et al.*, 1983). Long-term survivals are seen in patients with early stage, well differentiated tumours. Since many of these tumours are high grade and are diagnosed at an advanced stage, they generally carry a poor prognosis. Radical cystectomy is the treatment of choice with or without prior radiotherapy. The results of such treatment, however, will depend on the above-mentioned factors. The signet cell variety of adenocarcinoma has been uniformly reported to have a poor prognosis (Gonzalez *et al.*, 1982; Choi *et al.*, 1984; Blute *et al.*, 1989). The poorer prognosis of urachal adenocarcinoma has been explained on the basis of a higher degree of anaplasia and a more advanced stage of disease on account of its asymptomatic nature until a very late stage (Kakizoe *et al.*, 1983; Hayman, 1984). In the present series, however, urachal carcinomas, however small the number, were found to have a better prognosis than primary adenocarcinomas of the bladder.

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Neuro-endocrine Cells—A New Prognostic Parameter in Prostate Cancer

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Summary—Neuro-endocrine cells are a recognised component of prostatic ducts and acini. Half of all clinically manifest cancers show neuro-endocrine differentiation. Occult carcinomas have a lower incidence of such differentiation. Neuro-endocrine cells are of major prognostic importance and appear more reliable in predicting patients' survival than do conventional histological grading systems.

Neuro-endocrine cells are a well recognised component of normal prostatic ducts and acini (Abrahamsson *et al.*, 1986). Approximately 50% of prostate cancers contain small numbers of neuro-endocrine cells (Di Sant'Agnese and de Messy Jensen, 1987; Cohen *et al.*, 1990) which can be demonstrated by silver and immunohistochemistry (Di Sant'Agnese and de Messy Jensen, 1987; Azzopardi and Evans, 1971). It has been suggested that tumours demonstrating neuro-endocrine differentiation have a worse prognosis than those not showing such differentiation (Cohen *et al.*, 1990). Neuro-endocrine positive tumour cells are indistinguishable on routine light microscopy from neuro-endocrine negative tumour cells.

Prognosis indicators in current use in prostate cancer include tumour stage (Jewett, 1975) and tumour grade (Gleason, 1977). Tumour staging appears to be readily reproducible and correlates well with patient survival. By contrast, grading systems are prone to individual subjectivity (Harada *et al.*, 1977) but are most accurate at predicting prognosis at the extremes of grade (well differentiated and poorly differentiated tumours). The vast majority of tumours, however, fall into the intermediate grades and have an unpredictable course (Cohen *et al.*, 1990). In addition, tumour response

to hormone manipulation cannot be accurately assessed by present-day prognostic indices.

The aim of this study was to correlate the prognosis of prostatic carcinoma with the presence of neuro-endocrine cells and to compare this variable with presently used prognostic indices, *i.e.* stage and histological grade. In addition, the neuro-endocrine differentiation of a subset of early prostate cancer (A1) was compared with that of more advanced tumours.

Patients and Methods

The study group comprised 110 patients selected sequentially from the hospital records at the Johannesburg General hospital from October 1981 to June 1986. The records indicated that all patients were subjected to prostatic biopsy, either by transurethral resection (TUR) or by needle biopsy (transrectal). In all cases the diagnosis was that of carcinoma stage B, C or D.

Twenty patients were excluded for the following reasons:

- (1) Five patients had died within 1 month of surgery. These deaths were attributed to pulmonary thrombo-embolic disease or to medical complications unrelated to the prostatic cancer.
- (2) Six patients were excluded because of lack of follow-up.

- (3) In 4 cases there was insufficient tissue for histological examination.
- (4) In 5 cases the original diagnosis of prostatic carcinoma was incorrect: transitional cell carcinoma (4), metastatic colo-rectal carcinoma (1).

The remaining 90 patients were followed up to the date of writing or date of death. In each case the cause of death had been documented and, where available, post mortem material was examined. Six patients died more than 4 years after the original diagnosis. In all 6 patients post mortem material and accurate clinical records showed that they had died of causes unrelated to their prostate cancers. These 6 cases were included in the surviving group.

Of the 90 cases studied, 77 were subjected to TUR and at least 2 representative blocks were selected for examination. In 9 cases, only needle biopsy material was available for assessment. A further 4 patients underwent initial needle biopsy and, because of obstructive symptoms, this was followed by TUR. In these 4 cases, both needle biopsies and TUR specimens were examined.

Thirty cases of (A1) occult adenocarcinoma were selected sequentially from the hospital records, from December 1988 to June 1990. All were found incidentally at TUR performed for benign prostatic enlargement. In every case tumour volume was less than 4% of the total tissue and was graded Gleason score 7 or less. Ten of these 30 patients were excluded because further sections of the tissue blocks failed to demonstrate any malignant tumour.

All patients with manifest local and regional disease (B and C) were treated initially by radiotherapy. All of those with disseminated disease (D) were subjected to an endocrine manipulation (orchiectomy, LH-RH agonists, or stilboestrol). No patient in this series died without some form of endocrine manipulation.

All specimens were fixed in 10% phosphate-buffered formalin and processed to wax paraffin. Three 2- μ m sections were cut and taken to aqueous solution through graded alcohols. One section was stained with routine haematoxylin and eosin for diagnostic purposes and histological grading. Two sections were submitted to immunoperoxidase staining—namely, polyclonal neuron-specific enolase (NSE; Dako) and monoclonal chromogranin A (ChA; Enzo). Both of these peroxidase stains are markers of neuro-endocrine cells (Lloyd *et al.*, 1984; Turbat-Herrera *et al.*, 1986).

Without knowledge of the clinical history or the

patients' records, the following information was recorded:

- (a) Haematoxylin and eosin stained sections were assessed (Gleason, 1977) as major and minor grade. In addition, a Gleason score was allocated to each case.
- (b) Sections stained for NSE and ChA were regarded as negative (no neuro-endocrine cells present) or positive (individual cells or groups of cells showing positive staining) (Fig. 1). Two of the 4 needle biopsies in which further material was available for examination showed no evidence of neuro-endocrine differentiation. Neuro-endocrine cells, however, were demonstrated on evaluation of the transurethral biopsy material. These 2 cases, therefore, were considered positive for neuro-endocrine cells. This observation confirmed the focal distribution of neuro-endocrine cells in prostate cancer. Thus a single needle biopsy may be inadequate in assessing neuro-endocrine differentiation. Two other important observations were noted: namely, the presence of neuro-endocrine cells in benign prostatic glands (Fig. 2), as well as positive staining of nerve twigs by NSE (Fig. 3). These positive-staining areas were noted but were disregarded in tumour assessment.

Results

At the time of follow-up (July 1990) 38 patients were alive at least 4 years after the original diagnosis. Another 6 patients had died of unrelated causes and were included in the total surviving population of 44; 46 patients had died of their prostate cancer. Of the 44 survivors, 5 demonstrated neuro-endocrine cells in their tumours. Of the 46 who had died as a result of their tumours, 42 demonstrated neuro-endocrine cell differentiation (Fig. 4). Of the 4 negative cases, 2 were represented by a single needle biopsy. The patients were classified according to stage (Fig. 5), Gleason major grade (Fig. 6), Gleason minor grade (Fig. 7) and Gleason score (Fig. 8). Clinical stage and the presence of neuro-endocrine cells were the most significant prognostic indicators ($P < 0.0001$), while histological grading (Gleason) was of less significance ($P = 0.1241$). Neuro-endocrine cells were assessed for each stage and proved to be a reliable prognostic indicator in all stages (Table).

Neuro-endocrine differentiation was demonstrated in 2 cases (10%) of the 20 occult (A1) carcinomas examined. Follow-up of these 20

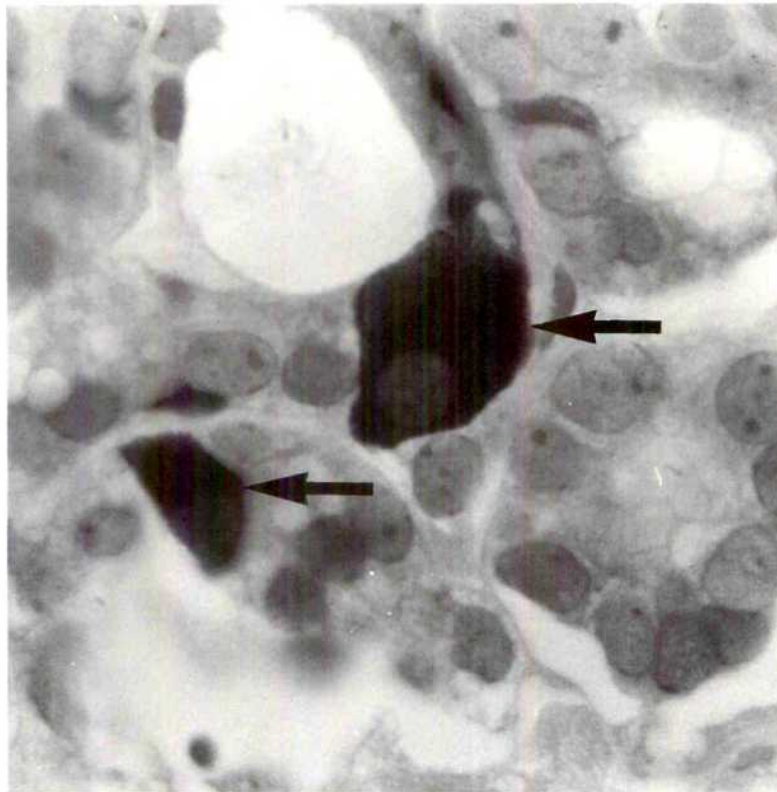


Fig. 1 Chromagranin-A positive-staining neuro-endocrine cells (arrows) in an otherwise unremarkable prostatic carcinoma ($\times 1320$; diaminobenzidine with haematoxylin counter-stain).

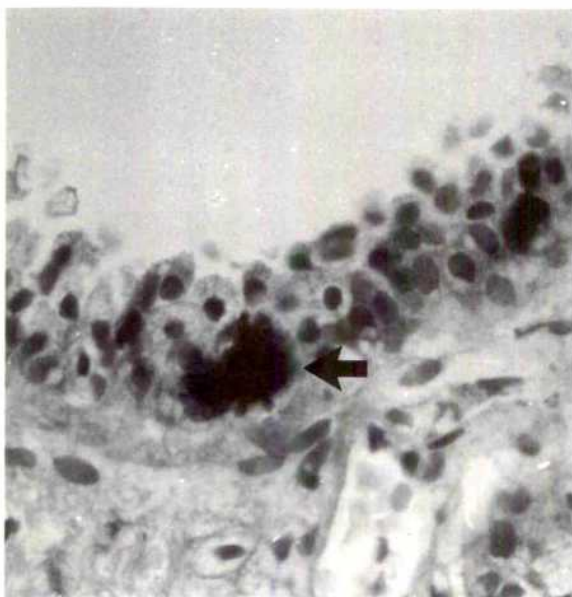


Fig. 2 Chromagranin-A positive-staining neuro-endocrine cells (arrow) in a benign prostatic gland ($\times 246$; diaminobenzidine with haematoxylin counter-stain).

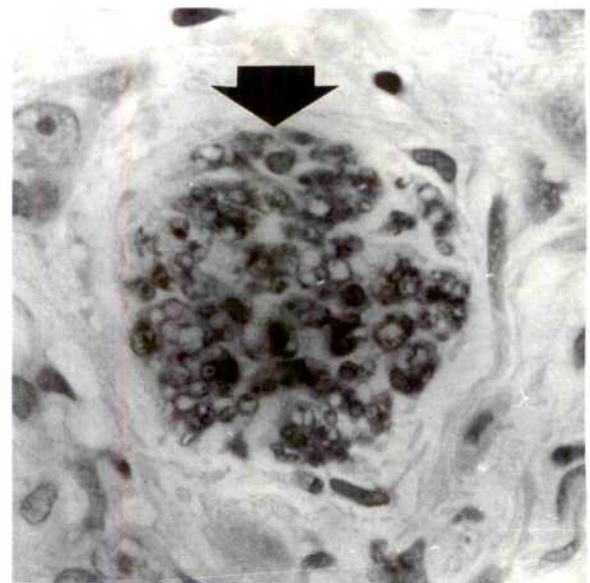


Fig. 3 Neuron-specific-enolase positive-staining nerve twigs with surrounding tumour cells showing no neuro-endocrine differentiation ($\times 1320$; diaminobenzidine with haematoxylin counter-stain).

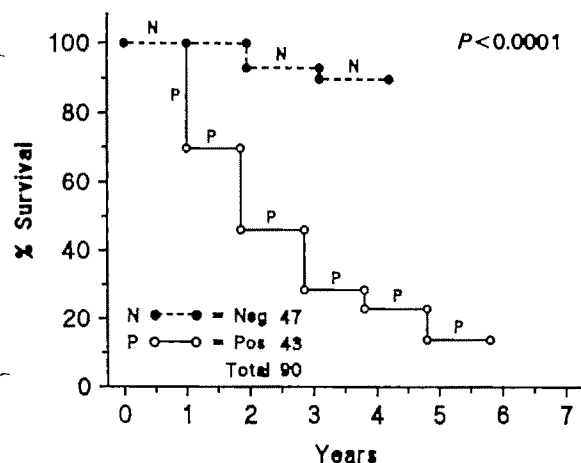


Fig. 4 Survival of 90 patients with prostate cancer, classified according to neuro-endocrine differentiation.

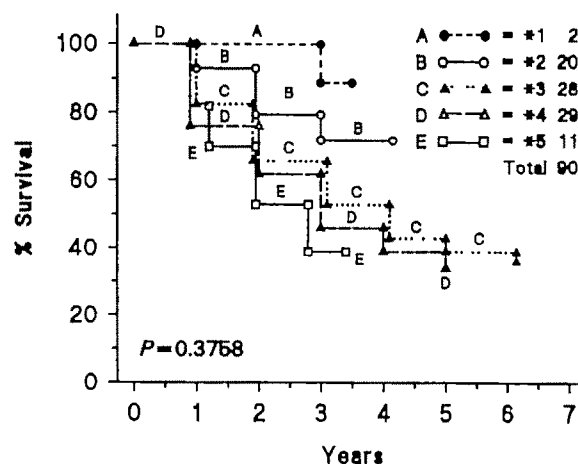


Fig. 7 Survival of 90 patients with prostate cancer, classified according to Gleason minor grade.

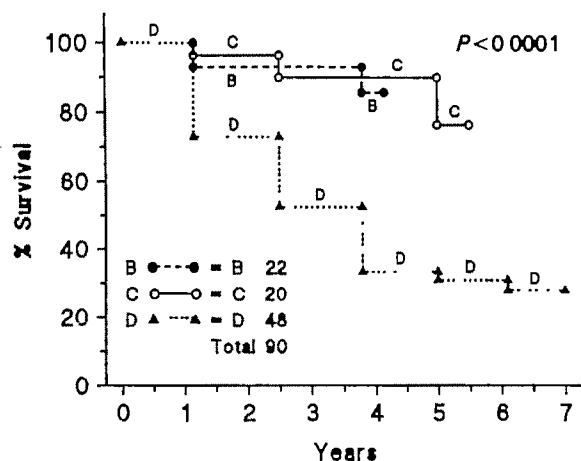


Fig. 5 Survival of 90 patients with prostate cancer, classified according to stage.

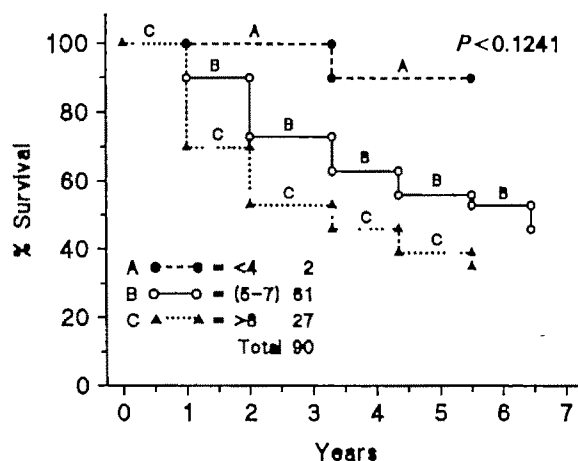


Fig. 8 Survival of 90 patients with prostate cancer, classified according to Gleason score.

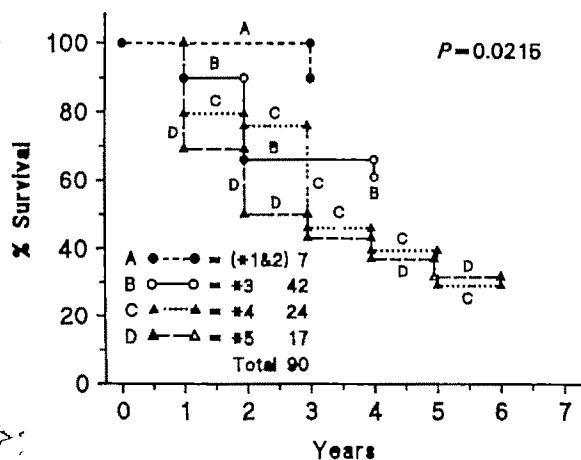


Fig. 6 Survival of 90 patients with prostate cancer, classified according to Gleason major grade.

Table Neuro-endocrine Cells in Stage-matched Disease

Stage	DOD	A/DOC
B—22*	4(3)	18(3)
C—20*	5(5)	15(2)
D—48*	37(34)	11(0)

* = Total numbers.

DOD = Dead of disease.

A/DOC = Alive or dead of other unrelated causes.

() = Positive for neuro-endocrine cells.

patients does not exceed 2 years, however, and no evidence of tumour progression has been noted in any single case.

Discussion

This study confirms the findings of other authors that approximately 50% of clinically manifest prostate cancer shows neuro-endocrine differentiation. Not one case resembled a carcinoid tumour or small cell carcinoma on histological examination. In early prostate cancer (pre-clinical A1), the incidence of neuro-endocrine cell differentiation is approximately 10%. This finding suggests that the neuro-endocrine cells are of importance in tumour progression. In addition, the prognostic importance of neuro-endocrine cells in stage-matched disease is demonstrated. This prognostic factor was significantly superior to the Gleason grading system.

In view of these findings it is suggested that the presence of neuro-endocrine cells be considered an independent prognostic variable. The precise role of these particular tumour cells is unknown, but it is speculated that these cells, like neuro-endocrine cells in other tissues, secrete peptide hormones which then influence the growth of tumour cells and allow these to escape androgen blockade. Neuro-endocrine cells are influenced by other peptide hormones, including somatostatin (Wilson, 1985) and this should be considered in future therapeutic trials. In the evaluation of current therapeutic modalities it is essential that the neuro-endocrine status of each tumour be assessed. Neuro-endocrine negative tumours have a significantly better short- and long-term prognosis than neuro-endocrine positive tumours. Therapeutic benefits, therefore, must be assessed separately in each group.

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Screening for Prostate Cancer. Comparison of Transrectal Ultrasound, Prostate Specific Antigen and Rectal Examination

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Summary—In seeking to define the relative value of transrectal ultrasound (TRUS), prostate specific antigen (PSA) and digital rectal examination (DRE) in the diagnosis of prostatic cancer, 863 patients were studied and the findings compared.

DRE detected malignancy in 0.3% of the population of asymptomatic "normal" men undergoing routine health screening, and in 1.6% of patients who consulted their General Practitioner for one reason or another. In patients who attended our out-patient department with a variety of urological symptoms (not necessarily prostatic), TRUS suggested malignancy in 2% of those glands which were pronounced normal on DRE. Significantly elevated PSA detected malignancy in 0.3% of the patients undergoing routine health screening. (Although this figure equals the pick-up rate by DRE in this group, they were not necessarily the same patients). When these 3 investigations are summated, the pick-up rate is twice as high as when a single parameter is used.

The natural history of prostatic cancer is unknown. McNeal *et al.* (1966) suggested that the capacity of prostate cancer to metastasise was a function of its volume. Even if tumour volume correlates well with the Gleason grade, the degree of capsular or seminal vesicle penetration, or even the extent of metastases, tumour volume *per se* is not an indicator of likely progression. George (1989) showed that 16% of T2-T3 tumours did not progress during a 7-year follow-up, and only 13% metastasised.

This lack of a predictor of the biological behaviour of prostate cancer makes any screening programme irrelevant unless a randomised study, including a control group of patients not subject to screening, has been carried out. Moreover, if we are unable to define the benefit of a screening programme for the population at risk (men over 50), the sensitivity of the most common and non-invasive diagnostic tests for this disease must be better defined.

Patients and Methods

We have studied the 3 most common investigations: digital rectal examination, transrectal ultrasound and prostate specific antigen.

The value of digital rectal examination

Two separate studies were undertaken.

The first group (group 1a) was studied over a 6-month period and concerned a population of 863 asymptomatic men between 50 and 60 years of age who were attending for a routine quinquennial health check.

The second study (group 1b) was conducted on a population of men consulting their General Practitioner for a multitude of symptoms, not necessarily urological. The purpose of the study was explained to them: only 70% (370 patients) agreed to submit to DRE.

The value of transrectal ultrasound

From October 1988 to April 1989, 481 new patients attended our out-patient clinic. Their average age

was 67.2 years. All of these patients (group 2) underwent a rectal examination and a transrectal ultrasound scan of the prostate at the time of their consultation. The study was done prospectively. Those who had abnormalities either on DRE or on TRUS were submitted to ultrasound-guided transperineal prostatic biopsy.

The place of PSA

PSA was evaluated as a screening procedure on a population of 863 men aged 50 to 60 years (group 3). Those with an elevated value were re-examined by a urologist and if the DRE was abnormal prostatic biopsy was carried out.

Results

Table 1 shows that in the asymptomatic population the DRE was abnormal in 20% but the malignant pick-up rate was 0.34%.

In group 1b (Table 2), 59 of 320 DREs (16%) were abnormal and histological confirmation of malignancy was obtained in 6, giving a pick-up rate of 1.6%.

Table 3 shows that an abnormal DRE (in the out-patient clinic population) had a predictive value of 51%, but when an abnormal DRE was corroborated by abnormal ultrasonography the predictive value rose to 58%.

With regard to the value of PSA estimation, of the 38 patients with a raised value, biopsy proven

Table 3 Results of Digital Rectal Examination/Transrectal Ultrasound in 481 Patients

	No.	Benign	% benign	No. of tumours	Positive predictive value (PPV) %
DRE-/TRUS-	231	215	93	16	7
DRE-/TRUS+	135	127	94	8	6
DRE+/TRUS-	17	15	88	2	12
DRE+/TRUS+	98	57	58	57	58
DRE+	115	72	62	59	51

malignancy was found in 3, giving a predictive value of 8% and an overall detection rate of 0.3% (3/863).

Discussion

From our first cohort (Group 1a), it would appear that the percentage of abnormal prostates on DRE in the population screened was 20% but the detection rate for prostatic cancer only 0.34%.

Faul (1982) examined 1000 "normal" men over the age of 45 and found abnormal prostates on DRE in 16% but his detection rate for prostatic carcinoma was 2%. This difference in pick-up may be explained by the fact that in our series the upper age limit was 60. Thompson *et al.* (1984) had a detection rate of 0.55% in a population between 40 and 70 years old.

Our low detection rate in this group (note the upper age limit of 60) implies that simple DRE as a screening technique is not justified.

In group 1b (Table 2), 59 rectal examinations were abnormal (16%) and 6 localised carcinomas were found on biopsy, giving a detection rate of 1.6%. Such a figure (1.3%) had already been reported by Lee *et al.* (1988) in a self-referred population of 784 men and a figure of 1.8% was reported by Chodack and Schornberg (unpublished data) in 2139 patients undergoing routine screening. In all of these series the DRE was undertaken by General Practitioners as part of their routine physical examination.

In Group 2 (DRE + TRUS) the results show that when the DRE was abnormal, ultrasound guided biopsy was positive in 50%, giving a detection rate of 12%. By contrast, when the DRE was normal a hypoechoic lesion had a positive predictive value of 6% with a detection rate of 1.6%. This very low rate makes any massive screening programme based on ultrasonography an expensive waste of time.

Table 1 Prostate Findings in 863 Asymptomatic Patients

Digital rectal examination	No.	%	No. of biopsies	No. of tumours
Normal	697	80	0	0
B.P.H.*	105	12	10	0
Firm	37	4	6	1**
Nodular	24	3	5	2†

* B.P.H. = benign prostatic hyperplasia.

Patients' ages: ** 55 years; † 58 and 60 years.

Table 2 Prostate Findings in 370 Patients Consulting their General Practitioner

Digital rectal examination	No.	%	No. of tumours
Normal	311	84	
Suspicious	59	16	6*

Patients' ages: * 61, 63, 67, 70, 72, and 76 years.

When both DRE and TRUS were positive, the predictive value of a hypoechoic lesion was 58%, a figure to be compared with 43.2% quoted by Cooner (unpublished data) and 62% quoted by Lee *et al.* (1989) (Tables 4 and 5).

In the present series there were 24 T1-T2 tumours but only 8 of these were detected by ultrasound, *i.e.* two-thirds of these early carcinomas were normal according to DRE and TRUS.

Table 6 shows that 4.4% of the men studied had an abnormal PSA value. A similar figure was

reported by Myrtle (unpublished data). In this group only 3 patients were found to have carcinoma on biopsy and they all had abnormal findings on DRE. In other words, PSA plays no part in a screening programme.

Digital rectal examination is currently as useful an examination as any in the detection of asymptomatic prostatic cancer.

Transrectal ultrasonography should not be used as a screening tool but it does double the detection rate by picking up cancer in clinically normal glands. In the further elucidation of the clinically abnormal gland its value is unquestioned, but this is not the same as screening.

As a screening tool PSA estimation alone is valueless.

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Table 4 Results of DRE and Ultrasound Guided Biopsy According to Cooner (unpublished data)

	No. of patients	No. of patients with cancer	Positive predictive value (PPV) %	Detection rate %
DRE+	565	203	43.2	35.9
DRE-	1242	60	16.4	4.8
Total	1807	263	31.5	14.6

Table 5 Results of DRE and Ultrasound Guided Biopsy According to Lee *et al.* (1989)

	Biopsy	Number of patients with cancer	Positive predictive value (PPV) %
DRE+	114	71	62
DRE-	104	33	32
Total	256	104	40

Table 6 Serum PSA and Detection of Prostate Cancer

DRE	No. of patients	PSA > 4	%	No. of patients with cancer
Normal	697	23	3.2	
B.P.H.	105	9	8.5	
Firm	37	3	8	1*
Nodular	24	2	8	2†
Total	863	38	4.4	3

Patients' ages: * 58 years; † 58 and 60 years.

Urethral Pressures: Analysis of Transmission Pressure Ratios

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Summary—Transmission pressure ratio (TPR) analysis of urethral pressure profilometry data has been advocated for the diagnosis of genuine stress incontinence (GSI). However, the clinical usefulness of the technique has not been adequately evaluated. Using videourodynamics as the gold standard, the TPR results of 150 continent women and 153 with GSI have been compared. The mean TPR for each quartile of the functional urethral length was computed, as was the maximum TPR value (TPR-max) and the position on the urethra where it occurred (TPR-mode). There was a statistically significant difference between the 2 groups for TPR values in the distal 2 quartiles of the urethra and for TPR-max and TPR-mode. With the use of the Kappa statistic it was found that the TPR-mode was the most discriminatory of the TPR parameters. Even using this measure, the overlap between normal and GSI was so great as to make accurate diagnosis impossible. It was therefore concluded that TPR analysis is useless for the diagnosis of GSI. However, such an analysis is helpful for the understanding of the pathophysiology of GSI and its treatment.

Advances in microtransducer technology have resulted in the widespread availability of a reliable and relatively cheap system for the simultaneous measurement of intravesical and intraurethral pressure (Asmussen and Ulmsten, 1975, 1976). Since continence depends on intraurethral pressure exceeding intravesical pressure even under stress (Enhörning, 1961), such a measuring system is theoretically ideal for assessing urethral sphincteric function and so could be used for the diagnosis of genuine stress incontinence (GSI).

Farghaly *et al.* (1985) stated, in a preliminary report, that urethral pressure profilometry (UPP) analysis of transmission pressure ratios is useful for the diagnosis of GSI. Again on theoretical grounds this is plausible as TPR is a measure of the relative transmission of the cough impulse to the urethra and bladder.

$$\text{TPR} = \text{U/B} \times 100$$

where U = cough impulse in the urethra
B = cough impulse in the bladder

It has been reported that the urethral TPR profile in women with GSI is different from that in asymptomatic women (Hilton and Stanton, 1983). Women with GSI have been shown to have a lower TPR than continent women but if this parameter is to be used diagnostically, the distributional overlap has to be minimal. With regard to this, a cut-off point should be determined for the TPR measurement to classify a test as positive for sphincter incompetence. Richardson (1986) considered the presence of a positive area under the stress profile as indicative of sphincter competence. However, Bump *et al.* (1988) reasoned that the use of a more sophisticated analysis when examining TPRs led to better discrimination between patients with GSI and those with competent sphincters.

The aim of this study was to discover the most discriminatory TPR parameter and its threshold

value for the diagnosis of GSI. Further statistical manipulation of the data was aimed at delineating the efficacy of this cut-off point by calculating the 2 types of errors (false positives and false negatives). The continent population consisted of women who were urodynamically normal on pad testing and videourodynamics (VCU), whilst the incontinent group were women with a VCU diagnosis of GSI alone (*i.e.* a stable bladder but with sphincter incompetence).

Patients and Methods

All patients presenting to the urodynamic clinic with urine that was negative to microscopy and culture underwent pad testing (Versi and Cardozo, 1986), uroflowmetry, VCU (Bates *et al.*, 1970) and UPP studies. The urodynamic diagnosis was based on pad testing, uroflowmetry and VCU and the women in whom no abnormality was detected acted as the control group ($n = 150$). Those with GSI ($n = 153$) were regarded as the test group, the groups being matched for age and body mass index (weight divided by height squared). Women with a third degree prolapse or previous incontinence surgery were excluded from the study.

Urethral pressure profilometry was carried out on all women according to the technique described by Hilton and Stanton (1983). A Gaeltec 7 F catheter with 2 solid state depressed transducers mounted 6 cm apart was used for recording the urethral pressure with a lateral orientation at a withdrawal speed of 2.5 mm/s. The women were assessed in the supine position with 250 ml physiological saline in their bladders. At least 2 resting profiles were obtained to ensure reproducibility and stress profiles were then obtained in the same manner. The patients were asked to cough repeatedly during withdrawal of the catheter and the final profile was used for the analysis.

Unless otherwise stated, all terms describing urodynamic tests conform with the standards set out by the International Continence Society (Abrams *et al.*, 1990).

Analysis

The size of the cough impulse was measured from the bladder and urethral trace and so the ratio (TPR) was calculated. This was repeated for every cough registered over the functional length of the urethra. For every patient the functional urethral length was divided into quartiles and the mean TPR obtained for each quartile. The overall mean TPR was then calculated for each quartile and the

results are shown in Table 1. This method ensured that patients with a greater number of coughs in a given quartile did not bias the overall result. For every subject the maximum TPR value (TPR-max) was determined, as was the distance from the bladder neck along the functional urethra where it occurred (TPR-mode).

Kappa (Cohen, 1968; Landis and Kock, 1977; Versi *et al.*, 1986b) is a statistic that measures the agreement between tests. The maximum value that Kappa can attain is unity when the agreement is perfect and the higher the value of Kappa, the smaller the errors (false positives and false negatives). This statistic was used to determine which TPR parameter (and at what cut-off point) yielded the greatest agreement between VCU and UPP findings. Taking the VCU findings as the gold standard, the point where Kappa was maximum (in any given quartile of the functional urethra) was taken as the optimum value for the TPR cut-off point for that quartile. The greatest maximum Kappa indicated the most discriminatory variable.

The analysis was carried out as follows. The computer was programmed to rank all of the values for every TPR variable for both groups (continent and GSI) from low to high. The next step was to create 2×2 tables by sequentially dividing the data into low-high by starting at the lower end. For each division the computed 2×2 table gave the false positives, false negatives, sensitivities and specificities for that cut-off point. For each 2×2 table Kappa was computed as follows:

$$\text{Kappa} = (\text{Po} - \text{Pe}) / (1 - \text{Pe})$$

where P = (true positives) + (true negatives) divided by the total number of patients assessed.
where o = observed data and e = expected values

In this way a cut-off point for each variable was determined to yield the maximum Kappa and hence the best discrimination for that TPR parameter

Table 1 Comparison of TPR Values in Continent Patients and Those with GSI

Parameter	Mean ($\pm$ SD)		Statistical significance
	Continent	GSI	
First quartile	87 (17)	87 (13)	NS
Second quartile	84 (20)	81 (18)	NS
Third quartile	77 (25)	69 (21)	$P < 0.01$
Fourth quartile	48 (30)	42 (26)	$P < 0.05$
TPR-max	102 (19)	97 (23)	$P < 0.02$
TPR-mode	39 (26)	26 (22)	$P < 0.001$

NS: $P > 0.05$, no statistical significance.

(Table 2). The parameter with the greatest maximum Kappa was then deemed to be the most discriminatory parameter. Theoretically the cut-off point that yields the greatest Kappa can then be used most efficiently to distinguish continent from GSI patients on the basis of the UPP data.

Table 2 Optimum Cut-off Points and Maximum Values of Kappa for each of the TPR Parameters

Parameter	Cut-off value	Maximum Kappa
First quartile	95	0.038
Second quartile	95	0.104
Third quartile	85	0.157
Fourth quartile	79	0.132
TPR-max	100.5	0.195
TPR-mode	33	0.248

Results

In this study a comparison was made between 150 continent women and 153 patients with GSI. The mean TPR for the 2 groups in each quartile is shown in Table 1. The means for the first half of the urethra are not significantly different. The distal 2 quartiles are statistically significantly different but the standard deviations are so large that the overlap appears to be too great for these quartiles to be used for discriminating between continent and GSI patients.

To confirm this, the most discriminating cut-off points (of each parameter) were used to generate the efficacy data shown in Table 3. As can be seen from this Table, the discrimination is poor, with low sensitivities and high false positive and negative rates.

The variable measuring the distance along the functional urethra from the bladder neck where the TPR-max occurred (TPR-mode) yielded the highest values for Kappa (Table 2), *i.e.* of all the parameters

Table 3 Efficacy Data for TPR Cut-off Points shown in Table 2

Parameter	Sensitivity	FN	Specificity	FP
First quartile	45	55	60	40
Second quartile	47	53	70	30
Third quartile	50	50	70	30
Fourth quartile	48	52	84	16
TPR-max	51	49	71	29
TPR-mode	55	45	71	29

FP = false positive rates.

FN = false negative rates.

measured, this was the most discriminatory. The Figure shows the distribution of TPR-mode, comparing continent patients with those with GSI. Again the overlap between the groups is too great for even this parameter to be used for discrimination.

Discussion

This study set out to evaluate the use of TPR measurements for the diagnosis of GSI. It was assumed that the urodynamic diagnosis based on VCU was the correct diagnosis and so the latter posed as the gold standard against which UPP data were compared. The data set consisted of continent women and GSI patients. A total of 6 TPR parameters were examined to determine the most discerning measurement. The overlap between the 2 groups was least when TPR-mode was considered (Fig.). Even with this most discriminating parameter it was impossible to observe a clear demarcation between continent women and patients with GSI.

Measurements of the resting profile may not yield much information about urethral sphincter incompetence (GSI) because the latter is a dynamic failure of the sphincteric mechanism. It follows that the stress profile may be better for the diagnosis of GSI. Indeed in our earlier study (Versi *et al.*, 1986a) the most discriminatory parameter was the "area under the stress profile" with a maximum Kappa of 0.42. Even with this parameter the overlap was too great to be diagnostically useful.

It is known that the shape of the stress profile changes with the magnitude of the coughs. To compensate for this an analysis of the ratio of the cough impulse to the urethra and bladder (TPR)

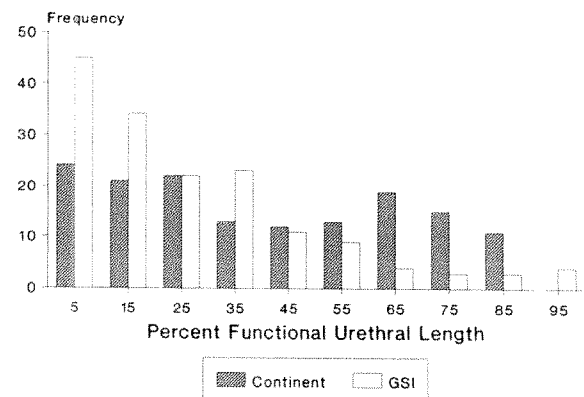


Fig. Distribution of TPR-mode for patients with GSI compared with those who are continent. Note that the 2 distributions are markedly different.

was considered in the hope that it would yield a more discriminatory test. The data presented in this report suggest otherwise.

Table 1 shows the difference between continent women and those with GSI in terms of the TPR values. Although there is a statistically significant difference between the 2 groups in the distal urethra, the distributional overlap is too great to allow any of the quartiles to be used diagnostically. Table 2 shows that all of the parameters measured are poor discriminators as no Kappa value is higher than 0.25. A Kappa value of 1.0 would signify a perfect test but values of less than 0.6 are unsatisfactory (Landis and Kock, 1977).

Bump *et al.* (1988) studied a smaller group of 110 subjects, including those with severe prolapse and previous incontinence surgery. Arbitrarily they considered cut-off points of 0.6, 0.7, 0.8 and 0.9 for TPRs in the proximal three-quarters of the urethra. They found that a cut-off point of 0.9 had "the best diagnostic accuracy". However, Kappa analysis of their data results in a value of 0.39, which is not very accurate. When our data were subjected to the same analysis, using a cut-off value of 0.9 for the proximal three-quarters of the urethra (Bump *et al.*, 1988), the Kappa value obtained was 0.09 with a specificity which was comparable (60% versus 56%) to that of Bump *et al.* (1988) but a much lower sensitivity (49% versus 97%). This suggests that many of our patients achieved TPRs > 0.9 but were still found to have GSI on VCU studies. The difference in our results may be explained by the possibility that our radiographic method of detecting sphincter incompetence was more sensitive than their method of "direct visualization for fluid loss". Nonetheless, the Kappa analysis is a more systematic method of approaching the problem and does allow for comparison of data from different units.

In every stress profile 1 cough will produce the maximum TPR and this cough will occur at a certain distance from the bladder neck. TPR-max is expressed as a percentage but many of the values exceed 100. This implies that the "cough" produced an intraurethral pressure higher than the intravesical pressure. This may be caused by the urethra being pushed against the symphysis pubis, as after a colposuspension (Hertogs and Stanton, 1985), or alternatively may be due to active contraction of the musculature of the urethra and/or pelvic floor (Constantinou, 1985).

The most discriminating parameter was TPR-mode, the position along the urethra where TPR-max occurs. In previous studies this parameter has

not been analysed for its discriminatory potential. Table 1 and the Figure show that patients with GSI had a TPR-mode which was more proximal than in continent women. Traditionally it has been taught that continence is maintained at the level of the bladder neck (internal sphincter) and the external sphincter (distal) acts as a backup system. It has been shown that about half of continent women during the climacteric have an incompetent bladder neck on coughing (Versi *et al.*, 1986b). Using the urethral electrical conductance probe, Janez (personal communication) obtained similar results in continent perimenopausal women but found that younger continent women had competent bladder necks and older continent women had a higher prevalence of bladder neck incompetence. These unpublished data suggest that bladder neck incompetence is age-dependent. It could be argued that bladder neck incompetence is the first step towards the development of GSI. Indeed we have shown that women with bladder neck incompetence maintain their continence by better use of their distal sphincter (Versi *et al.*, 1990), *i.e.* they have augmented distal TPRs and so the TPR-mode is located more distally.

Given the above, it is possible that during the genesis of sphincter incompetence the bladder neck is the first barrier (sphincter) to be lost but continence is maintained by the distal sphincter mechanisms (TPR-mode shifts distally). Subsequently these compensatory mechanisms may become inadequate and decompensation leads to incontinence. If this hypothesis is tenable, women with GSI should have a more proximally located TPR-mode as seen in these data (Fig.).

Physiotherapy for stress incontinence is aimed at improving pelvic floor musculature. On anatomical grounds these exercises should have their effect in the region of the distal urethra. We therefore postulate that physiotherapy works by reversing the decompensation (failure of the distal sphincter) that leads to incontinence. If this were true, then following physiotherapy for GSI, TPR-mode should be shifted distally in cases where therapy is effective. This model is amenable to experimental testing. Data from Finland (Kujansuu, 1983) support this hypothesis in that following pelvic floor exercises, improvement was seen only in the TPR of the distal urethra.

In this study the maximum Kappa was obtained for the TPR-mode parameter at a value of 0.25. In our earlier study (Versi *et al.*, 1986a) the maximum Kappa was 0.42 for the "area under the stress profile". This suggests that for UPP measurements

overall, the latter parameter is more discriminatory but even then the overlap is too great for the test to be used for the diagnosis of GSI.

In conclusion, the data from this study and from our earlier work do not support the proposition that any single UPP measurement can be used to diagnose GSI. Nonetheless there may be some value in analysing TPR data as a means of monitoring response to physiotherapy for GSI.

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Presentation and Management of Urethral Calculi

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Summary—A total of 36 patients with urethral calculi are presented; 34 were males, aged 2 to 65 years (mean 43). Eight patients were under the age of 6 years and presented with retention of urine. Calculi were in the posterior urethra in 56% of the patients, 33% had associated urinary tract calculi, and 47% had other diseases of the lower urinary tract, the commonest being posterior urethral stricture (42%). Of these calculi, 58% could be manipulated endoscopically into the urinary bladder, then crushed. Associated urethral strictures were dealt with by visual internal urethrotomy before manipulating the calculi. Other methods of treatment and their complications are discussed.

Although urethral calculi occur fairly commonly in developing countries (Koga *et al.*, 1990), reports are scanty. We report the pattern of urethral calculi in 36 patients treated over 5 years in the genito-urinary unit at Soba University Hospital, Khartoum.

Patients and Methods

All patients diagnosed as having urethral calculi between 1985 and January 1990 were included in the study. A detailed urological history was taken; physical examination included palpation of the urethra and rectal examination and a plain X-ray of the urethra and bladder region was obtained. A retrograde urethrogram was performed if associated urethral pathology was suspected. Urethral calculi were analysed with regard to symptoms, anatomical site, associated diseases and management. Follow-up ranged between 6 and 33 months (mean 9).

Results

A total of 36 patients with urethral calculi were analysed (34 male and 2 female). Their mean age was 43 years (range 2–65). All 8 patients under the age of 6 years presented with acute retention of

urine. Other presenting symptoms are shown in Table 1.

Twenty of the calculi in the male patients were in the posterior urethra, 10 were in the penile urethra and 4 in the fossa navicularis. Seventeen patients (47%) had associated diseases of the lower urinary tract, the commonest being urethral stricture (15 patients) (Table 2). The 2 female patients had had previous pharaonic circumcision and both had calculi in associated urethral diverticula. Twelve patients (33%) had associated urinary calculi; these were renal or ureteric in 8 and vesical in 4. Management of the urethral calculi is summarised in Table 3. The 8 patients presenting with acute retention of urine received urgent treatment. The urethral calculi were manipulated endoscopically into the urinary bladder; this was followed by vesicolithotomy in 5 children but in the

Table 1 Presenting Symptoms and Signs in 36 Patients with Urethral Calculi

Symptoms and signs	No. of patients
Dysuria	12
Interruption of urinary stream	10
Retention of urine	8
Urethral fistulas and sinuses	3
Palpable urethral mass	3
Total	36

Table 2 Associated Diseases of the Lower Urinary Tract in 17 Patients with Urethral Calculi

Associated disease	No. of patients
Urethral stricture	15
Urinary bilharziasis	4
Urethral diverticulum	4
Multiple urethral fistulas and sinuses	3
Total	26

Nine patients had more than one associated disease.

Table 3 Management of urethral calculi in 36 Patients

Management	No. of patients
Visual internal urethrotomy and Push-back, then litholapaxy	12
Retrograde manipulation, then Litholapaxy	9
Retrograde manipulation, then Vesicolithotomy	5
Removal through external urethrotomy	7
Extraction through the meatus	3
Total	36

remaining 3 cases the calculi could be extracted from the external urethral meatus. The 15 patients with urethral calculi and associated urethral strictures underwent visual and internal urethrotomy initially; the stones were then pushed into the bladder and crushed in 12 cases, while in 3 patients the stones were removed through a perineal urethrotomy either because the stricture was too tight or the stone too big. In the remaining 13 patients, 9 had retrograde manipulation of the calculus into the bladder followed by litholapaxy, while 4 also required external urethrotomy to deal with an associated diverticulum. There were 7 post-operative complications: Gram-negative septicaemia in 3, the tip of the Sache urethrotome knife broke in the urethral lumen in 2, 1 patient had urethral bleeding and another developed a urethral fistula 3 weeks after removal of the calculus.

Discussion

Urethral calculi in children were commoner in this study (22%) than in that reported by Koga *et al.* (1990). All of the children in this study presented with acute retention of urine. Amin (1973) reported a high incidence of retention (89%) but Paulk *et al.* (1976) and Selli *et al.* (1984) found it to be an uncommon occurrence. Calculi were in the poste-

rior urethra in 56% of patients; this is in agreement with the findings reported by Paulk *et al.* (1976) and Koga *et al.* (1990). The higher incidence of posterior urethral calculi in the present series is possibly related to the high incidence of post-inflammatory urethral strictures in the region of the posterior urethra (Sharfi, 1989). Associated urinary calculi occurred in 33% of the patients; this is similar to the incidence reported by Koga *et al.* (1990) and emphasises the importance of evaluating the upper urinary tract in patients with urethral calculi.

Management of the urethral calculi varied according to the site, size and associated urethral pathology. Retrograde manipulation into the urinary bladder, then litholapaxy, can be a safe procedure for posterior urethral calculi provided that the manipulation is done endoscopically under direct vision. A distal urethral stricture can be dealt with by visual internal urethrotomy before manipulating the calculus into the urinary bladder (Sharfi, 1989). Impacted, large irregular calculi or those in a urethral diverticulum are best removed through an external urethrotomy followed by excision and repair of the diverticulum. Extraction through the external meatus is suitable only for small, smooth calculi in the region of or distal to the fossa navicularis. Suarez (1985) reported that a urethral calculus could be engaged in a basket and pulled inside the urethroscope sheath, so that the stone, basket and sheath could be removed under direct vision. Durazi and Samiei (1988) reported successful ultrasonic fragmentation of impacted urethral calculi in 7 patients.

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The Role of Delayed Primary Repair in the Acute Management of Pelvic Fracture Injuries of the Urethra

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Summary—The principal aim of management of the ruptured urethra should be to do everything possible to reduce the long-term complication rate and this applies principally to stricture formation. By far the most difficult complication to treat is severe distraction; thus the aim of early management should be to recognise and correct severe distraction injuries. Delayed primary repair at 7 to 10 days is recommended for this problem. The aim is not to prevent a stricture occurring but to make sure that if it does occur it is easily treatable.

Pelvic fracture injuries of the urethra are rare, usually occurring in about 10% of all individuals who sustain pelvic fractures. In a recent major air disaster, there were 26 instances of pelvic fracture but not one urethral injury (W. T. Lawrence, personal communication). As a result of this rarity it becomes almost impossible for any one urologist to acquire sufficient experience in the management of pelvic fracture injuries of the urethra to be able to draw firm conclusions as to the best form of management. Consequently the early management of these injuries is controversial.

For many years the prevailing view was that pioneered by Mitchell (1968, 1975) and Morehouse *et al.* (1972) and promulgated more recently by McAninch (1990). Proponents of this view advise against urethral catheterisation for fear of making any urethral injury worse and introducing infection. They suggest suprapubic catheterisation and then the adoption of a "wait and see" policy, treating any stricture as and when it subsequently develops.

The alternative view favours early intervention and "realignment" in all patients with a ruptured urethra (Patterson *et al.*, 1983; Devine *et al.*, 1989).

This report relates our experience of the early management of these injuries and suggests that a more selective treatment policy might be more appropriate.

Patients and Methods

In the last 6 years we have accumulated 17 male patients aged 16 to 42 years with a pelvic fracture injury of the urethra with complete disruption of the urethra and distraction of the 2 ends. Of these, 4 were admitted to this hospital immediately after their injury, 7 were transferred here from the receiving hospital during the first 7 days after injury and in 6 instances the author went to the receiving hospital and treated the patient there. All patients have been followed up by the author personally. In all 17 patients the diagnosis of a distraction injury of the urethra was made by demonstrating a "pie-in-the-sky" bladder by intravenous urography or by ultrasound and then confirming the diagnosis of urethral disruption by ascending urethrography.

All patients underwent a laparotomy between 7 and 14 days after injury. The haematoma was evacuated from the retropubic space and the 2 ends of the ruptured urethra were sutured accurately together, ensuring mucosal apposition, usually with six 3/0 Vicryl sutures around a 16F silicone catheter. A suprapubic catheter and a retropubic wound drain were also placed. Where possible the omentum was brought down to fill the anterior part of the retropubic space.

Internal or external fixation of the pelvic fracture was undertaken by an orthopaedic surgeon in 3 instances when there was vertical instability of the pelvic fracture. Otherwise the pelvic fracture itself

was treated by immobilisation in bed, with or without limb traction.

Three weeks post-operatively a urethrogram was obtained to see whether the anastomosis had healed. The urethrogram was obtained either by slowly withdrawing the urethral catheter, injecting contrast gently under radiological control, or more recently by passing a 5F infant feeding tube alongside the urethral catheter and then injecting contrast material gently around and alongside the urethral catheter in the region of the anastomosis. If there was extravasation at the anastomosis the catheters were left for 2 further weeks or until healing was complete. When the urethral catheter was removed the suprapubic catheter was clamped for a trial of voiding and then removed when voiding had been satisfactory for 24 h.

Patients were checked symptomatically and by assessing their urinary flow rate 3 months post-operatively, 6 months post-operatively and 1 year post-operatively, at which time an ascending urethrogram and micturating cystogram were obtained. Radiological assessment was made at an earlier date if the patient had any indication of a recurrent stricture on the basis of symptoms or a declining flow rate. All patients have been followed up for at least 1 year.

Results

In all instances the puboprostatic ligaments were more or less completely ruptured and the bladder and prostate appeared to ride up on the anterior surface of the rectum as though they were pulled up by the lateral vascular pedicles and as though the anterior rectal fascia, and below that the perineal body, acted as a barrier to any posterior spread of the disrupting force. In all instances it was possible to evacuate the retropubic haematoma without any significant re-bleeding. In all instances the haematoma extended through the pelvic floor into the perineum and in all instances the distal end of the urethra had retracted into the perineum and had to be pushed into view by manual pressure on the perineum.

In 12 instances the site of rupture was immediately sub-prostatic but in 5 cases the site of rupture was significantly lower, involving the bulbar urethra as much as the membranous urethra.

In all instances it proved possible to place 6 anastomotic sutures satisfactorily, although it would have been much easier to do so in those patients operated on more than 10 days after injury had the repair been attempted earlier.

None of these patients has yet required definitive treatment for a urethral stricture by urethroplasty, although 1 patient has required a urethrotomy and 2 have required urethral dilatation, all 3 at 6 months after their original injury and repair.

At the time of writing 5 patients are potent. What the incidence of potency would have been had they not been treated by delayed primary repair is impossible to say. It is also possible that 3 patients who have been treated more recently may still recover potency.

Discussion

Not only are pelvic fractures of the urethra in general rare, but serious injuries are very rare. It is only through the kindness of colleagues who are aware of our interest in the subject and who have referred their patients to us that we have accumulated the (relatively) small number of 17 patients with distraction injuries. By contrast, most pelvic fractures and the associated urethral injuries seen in an unselected population are relatively minor, often as a result of a fall at work, causing only a mild partial injury with no other significant problem. Such patients can be managed expectantly to see if they can void spontaneously; if not, percutaneous suprapubic catheterisation can be undertaken, treating any subsequent stricture as and when it develops. Such patients are not a problem and it is sensible to avoid urethral catheterisation for fear of making the relatively minor injury worse either directly by catheter-tip trauma or indirectly by introducing infection, unlikely though both these eventualities are under controlled conditions.

The problem lies at the other end of the spectrum with the multiply-injured patient whose life is in immediate danger. Here we feel that the importance of knowing the extent of the patient's injuries and of urgently establishing urinary drainage to monitor the adequacy of resuscitation outweighs the potential traumatic and infective risks of a *gentle* attempt at urethral catheterisation. If successful, it is of immediate diagnostic and therapeutic benefit. If unsuccessful, it is difficult to believe there is much chance in such a patient that matters have been made substantially worse.

If one gentle attempt at catheterisation fails, a percutaneous suprapubic catheter is inserted. The patient is then treated conservatively along the lines described by Mitchell (1968, 1975) and Morehouse *et al.* (1972). In this group of patients (without distraction) one can assume that if the patient does develop a stricture, it can be treated

quite simply (McAninch, 1990). At worst a simple transperineal anastomotic urethroplasty will be required and a good result can be expected. Indeed the success rate of transperineal bulbo-prostatic anastomotic urethroplasty approaches 100% (Turner Warwick, 1988). If there is any difficulty with this, it is assumed that the bladder is either empty or ruptured or in the wrong place—and specifically displaced upwards by a distraction injury. An ultrasound examination (or intravenous urogram) will show whether the bladder is empty or displaced. If it is empty, which is rare, and does not fill with time, then bladder rupture can be diagnosed. This is then treated by repair of the bladder and suprapubic catheterisation. If a laparotomy is required for bladder rupture (with or without other procedures) we would advise against attempting to deal with the urethra unless obviously distracted but without active bleeding into the retropubic space, which is an unlikely combination.

If the imaging study shows that the bladder is displaced upwards, indicating a severe distraction injury of the membranous or bulbo-membranous urethra, then a satisfactory outcome comparable to the results of transperineal anastomotic urethroplasty for strictures without distraction is much less likely. The patient is likely to end up with a long stricture which stretches the technique and therefore the success rate of anastomotic urethroplasty to its limit, depending as it does on the elasticity of the bulbar urethra to gain at best about 4 cm in length and generally only 2 or 3 cm (although there are ways of avoiding this, such as re-routing the urethra over one of the corpora cavernosa (Turner Warwick, 1988)).

For this reason we feel that the aim of early management of a ruptured urethra should be to identify and treat the "pie-in-the-sky" bladder, not to prevent a stricture developing (although this, of course, would be ideal) but so that any stricture that does develop can be treated simply, as in the less severely injured group. In this group of patients, and only this group, we feel that early reconstructive surgery is indicated to reapproximate the distracted ends of the urethra.

Some might argue that early reconstructive surgery might risk damage to the neurovascular bundles responsible for potency on the posterolateral aspects of the prostate and membranous urethra. Whereas this may be true under the relatively uncontrolled circumstances prevailing immediately after injury, it should not apply in the more controlled circumstances of delayed primary repair. Indeed delayed primary repair, when the

view is no longer obscured by the bleeding of the initial injury but before fibrosis has started to appear, is less likely to damage the neurovascular bundles than subsequent repair of an established stricture when the anatomy has been obscured by fibrosis.

It might also be argued that such surgery could just as easily be carried out immediately after the causative injury, but immediate intervention runs several risks. Firstly, opening the retropubic space may be met with torrential bleeding, having disrupted the tamponade effect normally present. Secondly, visibility with even moderate bleeding is obscured. Thirdly, the urological injury takes a low priority compared with potentially life-threatening injuries such as rupture of the liver or spleen or both. Fourthly, a urologist may not have been involved at this stage and, finally, irrespective of early management, some patients die during the early post-operative period because of the consequences of their injury. On the other hand, waiting much more than 14 days leads to fibrosis of the displaced strictures, so that the ability to reapproximate the ruptured ends is lost.

We therefore feel that patients should be operated on at 7 to 10 days, when they are more likely to be in relatively good general condition and can be prepared for an elective operation. Then the haematoma can be evacuated without much fresh bleeding and the 2 ends of the urethra can be brought together whilst the tissues are still supple enough to be sutured together without tension, before fibrosis has begun to pull them apart.

In practice this seems to have worked well, with a surprisingly low incidence of long-term problems. It should be stressed, however, that the aim of this report is not to show how low the incidence of stricture formation is—indeed some of these patients may go on to form strictures in the longer term. If they do, however, the strictures will be easier to treat than they might have been had the "pie-in-the-sky" bladder not been corrected. On the other hand, the selective use of primary repair for just this group of patients avoids the risk of unnecessary surgery in patients who would have healed up with at worst a short stricture, easily amenable to routine treatment.

The role of internal or external fixation of the pelvic fracture in relation to the urological injury has not been clearly defined. In general, fixation is used more frequently now than it was 10 years ago, but orthopaedic departments seem to vary widely in their inclination to intervene. Pelvic fractures are classified into (1) stable, (2) rotationally unstable

but vertically stable, and (3) rotationally and vertically unstable. About 90% are stable and do not usually require fixation. The majority of the remainder may perhaps be best treated by fixation but if they are vertically stable and not significantly displaced, many orthopaedic surgeons seem happy to rely on bed rest and limb traction. Only when the posterior sacroiliac ligamentous complex is ruptured and there is vertical instability is fixation of the fracture commonly used.

How this influences management of the urological injury is not clear (except for the technical point that it is sometimes difficult to reapproximate the urethra or indeed perform any surgical procedure within the pelvis after some types of external frame have been applied). Some authors describe the necessity of dividing the bony attachments of the prostate, mainly the puboprostatic ligaments, to gain access to the site of rupture and to prevent post-operative re-distraction (Devine *et al.*, 1990) should the bone fragments move. Our experience is that when the bladder is grossly displaced, the puboprostatic ligaments are already disrupted more or less completely and therefore do not need to be divided; conversely, if the ligaments are intact then the bladder will not be significantly displaced and the injury does not require surgical intervention in

the first place. It would therefore appear that the pelvic fracture should be treated on its own merits; if fixation is advised by the orthopaedic surgeon, however, its timing should be co-ordinated with the urologist.

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The Intraurethral Catheter: Long-term Follow-up in Patients with Urinary Retention due to Infravesical Obstruction

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Summary—Insertion of 43 intraurethral catheters (IUC) was performed on 31 patients in order to replace an indwelling catheter for urinary retention due to benign prostatic hyperplasia. The insertion of the IUC was done under local anaesthesia with lignocaine jelly in the out-patient clinic. The device has been in place for 3 to 14 months (mean 7), in 14 cases for > 3 months and in 29 cases for > 6 months. In 7 of the 43 inserted IUCs the device had to be removed earlier than intended (after 4.2–8 months) for reasons related to the device. Of the remaining 36 devices which were functioning well, 6 were removed at prostatectomy 3.5 to 8 months after insertion and an additional 6 IUCs had to be removed for reasons not related to the device; 24 IUCs are still in place and functioning satisfactorily. The mean maximal flow rate in these patients is 13.9 ml/s. Of the 31 patients, 27 had a positive urine culture before IUC insertion. None of the patients with the IUC had a clinically evident urinary tract infection, although in 7 cases the urine culture was positive during the follow-up period. All patients were in a better psychological state, and those who were able to perform sexually before they had the indwelling catheter were also able to perform sexually with the device in place. After long-term follow-up, the IUC has proved to be a cost-effective, successful alternative to an indwelling catheter and can be used as an alternative to prostatectomy in patients who are at high risk for surgery.

The indwelling catheter is a necessary tool for the relief of urinary retention in patients with complete infravesical obstruction or whenever a large volume of residual urine may endanger renal function. Because of the disadvantages and possible complications of the indwelling catheter, an intraurethral device has been designed and inserted into the posterior urethra as an alternative to the catheter. This special device has been in use since October 1988 and the results of early follow-up in a small group of patients have already been reported (Nissenkorn, 1989; Nissenkorn and Richter, 1990). Our experience with the use of 43 intraurethral catheters after long-term follow-up is reported.

Patients and Methods

The intraurethral catheter (IUC) (Puroflex-Urosoft, Angiomed, Germany) resembles a double Malecot 16F polyurethane catheter with a crown-like proximal end. It is now available in lengths of 35, 45 and 60 mm (Fig.) and it was designed to be placed in the bladder neck and prostatic urethra. The insertion technique has been previously described (Nissenkorn, 1989; Nissenkorn and Richter, 1990). The IUC was inserted, under local anaesthesia with lignocaine jelly in the out-patient clinic, in 31 men with urinary retention because of benign prostatic hyperplasia (BPH), and these were followed up closely for 3 to 14 months. The mean age of the patients was 73.5 years (range 54–100).

Antibiotic therapy, according to urine culture, was started 24 to 48 h before insertion of the IUC and continued for 5 to 7 days. Patients were advised

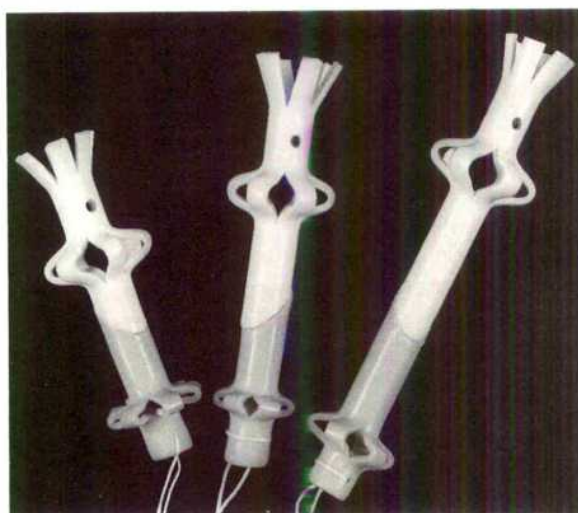


Fig. Intraurethral catheter, available in 35, 45 and 60mm lengths.

to have their IUC changed after approximately 6 months, in order to study possible changes in the device's structure and the local characteristics of the bladder neck and prostatic urethra. The patients were followed up closely and questioned regarding frequency and urgency of micturition and continence during day and night. Urine cultures were taken weekly during the first 2 weeks, then monthly, and ultrasound (to measure residual urine) was performed twice weekly during the first 2 weeks, then every month.

Results

The indications for IUC insertion were that 23 patients were considered a poor risk for surgery and 8 were on the waiting list for surgery (Table 1).

Of the 31 patients in the study, 12 agreed to have their IUC changed after 5 to 6.5 months. Thus a total of 43 IUCs were inserted in 31 men. During the follow-up period 19/43 IUCs were removed

Table 1 Indications for IUC Insertion in 31 Patients with an Indwelling Catheter

	No. of patients
Recent myocardial infarct	5
Recent cerebrovascular accident	8
Severe heart failure or obstructive lung disease	10
On waiting list for surgery	8
Total	31

(Table 2), 7 of which (16%) were for causes related to the device. A further 6 were removed at open prostatectomy 3.5 to 8 months after insertion. In 1 there was stone formation on the infravesical tip which did not cause obstruction. The remaining 5 showed no signs of encrustation.

In 6 patients the IUC had to be removed for reasons not related to the device. One patient complained of severe perineal discomfort and pain while sustaining an indwelling catheter. An IUC was inserted but there was no change in the symptomatology. After 6 months the IUC was removed and a catheter reinserted; the patient is still suffering from perineal pain, obviously not related to the IUC. Two patients who suffered from severe heart failure were admitted as emergencies and treated with a high dose of diuretics for acute pulmonary oedema. After 5 and 7.5 months of good function, the IUC was not able to cope with forced diuretics and a catheter had to be inserted because of high residual urine. In 1 patient the IUC has been pushed into the bladder, and a suprapubic catheter was inserted in the other patient. In another patient, who had the IUC for 4 months, the device became obstructed by stones after extracorporeal shock wave lithotripsy (ESWL). Two additional patients, although satisfied with the IUC after 7.5 and 14 months respectively, requested hyperthermia treatment of the prostate. In 7 patients (16%) the IUC had to be removed after 4.2 to 6 months (4 cases) and 6 to 8 months (3 cases) for reasons directly connected with the device. The reasons for removal were dislocation into the bladder (3), obstruction by clot (2) or suture (1) and stone encrustation (1) (Table 3).

No significant changes in the mucosa of the prostatic urethra were found either macroscopically during urethroscopy or microscopically on post-prostatectomy histology. In 2 IUCs there were encrustations (real stone formation in 1), which caused no urinary retention. One patient did not receive prophylactic antibacterial therapy before replacing the IUC and had high fever the same evening. Otherwise, no clinical evidence of urinary tract infection was found. Positive urine cultures were found in 7 cases (16%) during the follow-up

Table 2 Follow-up of 43 IUCs Inserted in 31 Patients with Benign Prostatic Hyperplasia

IUC removed	19
at prostatectomy	6
for reasons not related to IUC	6
for reasons related to IUC	7
IUC in place and functioning	24

Table 3 Reasons for Removal of IUC

Reason	No of patients
<i>Related to the device</i>	
Dislocation into the bladder	3
Obstruction by clot or suture	3
Stone encrustation (non-obstructive)	1
<i>Not related to IUC</i>	
Voiding failure after forced diuretics for pulmonary oedema	2
Requested hyperthermia of the prostate	2
Obstructed by stone after ESWL	1
Perineal pain and discomfort (continued also after IUC removal)	1

period of up to 14 months. Post-voiding residual urine was small (<50 ml) or absent in all patients. The mean maximal flow rate was 13.9 ml/s (range 12.5–19.5).

Although the patients suffered from frequency, urgency and sometimes urge incontinence during 2 to 4 days after insertion of the IUC, these symptoms disappeared and all were fully continent.

Discussion

The use of an intraurethral device (the iron gold-coated spiral) as an alternative to an indwelling catheter has been previously reported (Fabricius *et al.*, 1983; Fabian, 1984). In our opinion, the intraurethral polyurethane catheter reported here is a simpler, more physiological device, easier to insert and remove, and more economical than the metallic spiral.

The insertion of such a device has, to a great extent, solved the problems caused by the use of the indwelling catheter: urinary tract infection, urethral discharge, possible urethral stricture and a psychological burden for the patient. Most men with an indwelling catheter feel they lose dignity, are unable to perform sexually and are often unable to continue their routine life-style. Correct insertion of the IUC in patients with infravesical obstruction allows free voiding, complete bladder emptying, full continence, and should not interfere with normal sexual activity.

Insertion of the metal spiral has been performed either endoscopically (Fabian, 1984) or was ultrasonically guided (Nordling *et al.*, 1989). Although the IUC may also be inserted through a cystoscope sheath, its insertion with the insertion set may be as easy as the introduction of any common urethral catheter. The IUC is easy to remove in the event of malfunction.

In the present series of 31 patients, in whom 43 IUCs have been inserted, 84% of the devices functioned successfully. In 7 patients (16%) the device was removed for reasons related to the IUC, 4.2 to 8 months after insertion.

It was concluded that after long-term follow-up, the intraurethral catheter has proved to be a useful alternative to an indwelling catheter in patients with infravesical obstruction and to prostatectomy in high risk patients.

Because the possibility of encrustation and stone formation exists whenever a device or stent is in the urinary tract, it is suggested that the IUC be replaced every 6 to 7 months; this will prevent encrustation. To facilitate re-insertion, a catheter should be inserted after removal of the IUC for 2 to 3 days, then removed and replaced by a new intraurethral catheter.

Although there was no clinically evident urinary tract infection in the present series, urine cultures should be performed monthly and the patient should be treated by antibiotics in case of a positive urine culture, because infected urine might enhance encrustation or stone formation. The IUC is radio-opaque, and so a plain X-ray may help in determining the position of the IUC and in the diagnosis of possible stone formation. The relatively low infection rate in patients with an IUC (16%) is explained by the fact that only the prostatic urethra remains in contact with the device, leaving the membranous and penile urethra free of catheter.

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Cysts of the Tunica Albuginea—More Common Testicular Masses than Previously Thought?

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Summary—Cysts of the tunica albuginea have been considered very rare. Their clinical significance lies in their presentation as discrete testicular masses often diagnosed as malignancies prior to removal. We report our experience with 6 cases of cysts of the tunica albuginea over a 12-year period and review the relevant literature. It is obvious that these cysts can be both of epithelial and of mesothelial origin. Our material includes a cyst lined by a transitional-like epithelium, of a kind to our knowledge not reported previously. All of the cysts were found by palpation and they constituted 6% of the testicular tumours examined over the same period. High-resolution ultrasound examination can distinguish them from solid testicular masses, as in 2 cases here, thus enabling unnecessary operations to be avoided.

Cysts of the tunica albuginea have been considered rare and only 28 cases have been reported in the urological literature (Frater, 1929; Arcadi, 1952; Mancilla-Jimenez and Matsuda, 1975; Turner *et al.*, 1977; Mennemeyer and Mason, 1979; Sethney and Albers, 1980; Takihara *et al.*, 1982; Valvo *et al.*, 1983; Warner *et al.*, 1984; Mevorach *et al.*, 1985; Bryant, 1986). The use of ultrasound to screen scrotal diseases, however, has generated data to suggest that testicular cysts are not at all rare (Leung *et al.*, 1984; Gooding *et al.*, 1987). There has also been some controversy in the literature concerning the origin of cysts of the tunica albuginea (Arcadi, 1952; Mancilla-Jimenez and Matsuda, 1975; Mennemeyer and Mason, 1979; Bryant, 1986). We describe our experience with such cysts between 1976 and 1988 and review the relevant literature, with the aim of clarifying their origin.

Patients and Methods

The clinical records of all patients who underwent scrotal surgery from 1976 to 1988 were reviewed.

The surgery was performed because of a testicular tumour, defined as a palpable mass in the testis, in 105 cases (Table 1). Serum alpha fetoprotein and beta-HCG were measured pre-operatively and frozen section biopsies taken pre-operatively before orchiectomy.

Histological specimens were fixed in 10% phosphate-buffered neutral formalin and embedded in paraffin. Sections were stained with haematoxylin and eosin. Specimens from the tunica albuginea cysts were also stained with Alcian blue at pH 1 and pH 2.5 both with and without hyaluronidase

Table 1 Testicular Tumours Treated Surgically from 1976 to 1988

Testicular carcinomas	71
Benign germ cell tumour	2
Leydig cell tumours	
benign	1
malignant	2
Lymphomas	6
Metastasis	1
Infection/inflammation	7
Testicular necrosis	4
Cysts of the tunica albuginea	4
Epidermoid cyst	1
Adenomatoid tumours	7

treatment and periodic acid Schiff (PAS) with and without diastase treatment. Additional sections were stained with antibodies to cytokeratin (PKK1, Labsystems, Helsinki) and carcino-embryonic antigen (CEA) (Dako, Copenhagen) by the peroxidase-antiperoxidase method.

A total of 818 hemiscrotums of 414 patients with a suspected scrotal disorder were examined by ultrasound (7.5 MHz) between 1986 and 1988. No scrotal surgery was undertaken until an ultrasound examination had been performed.

Results

Four of the 105 patients who underwent surgery for a testicular tumour had a cyst of the tunica albuginea (Table 1). Since 1986, high-resolution ultrasound has been routinely used to examine all scrotal disorders, and 2 more patients with cysts of the tunica albuginea were found by this means. They were not treated surgically, but one was monitored by ultrasound and the other was verified at autopsy. It was estimated that tunica albuginea cysts constituted about 6% of all testicular tumours. In addition, 5 intratesticular cysts and 3 cysts of the tunica vaginalis were found by ultrasound.

Case reports

Case 1. A 35-year-old man had found a mass with occasional tenderness in his right testis 1 year earlier. There had been no increase in size. Otherwise the history was unremarkable.

On physical examination a firm, non-tender, non-transmitting, pea-sized nodule was noted on the lateral middle aspect of the right testis. A 6 mm cyst of the tunica albuginea was excised and the tunica albuginea was closed.

Case 2. A 32-year-old man had discovered a mass in his right testis 5 months earlier. There had also been some mild tenderness but no increase in size. History revealed nothing relevant. On physical examination a nodule was palpated in the area of the lateral middle aspect of the right testis. The patient was hospitalised to rule out testicular carcinoma.

At operation a 1-cm cyst and 4 cysts measuring 2 to 3 mm were found in the aforementioned position on the surface of the tunica albuginea. All were excised *en bloc* and were found to be filled with a serous clear fluid. The tunica albuginea was closed.

Case 3. A 36-year-old man had found an asymptomatic mass in his right testis 3 weeks earlier. He had no history of urogenital disease. On examination a firm nodule was observed on the inferior medial aspect of the right testis and carcinoma was suspected.

After the tunica vaginalis had been opened a smooth, hard cystic structure 7 mm in diameter filled with grey fluid was identified on the surface of the tunica albuginea. It was excised and the tunica albuginea closed.

Case 4. A 28-year-old man had palpated a mass in his left testis 5 months earlier in which he occasionally felt mild pain. History revealed no urogenital disease. The only finding of note was a small, non-tender mass in the inferior medial aspect of the left testis.

Testicular carcinoma was suspected and surgical exploration revealed a 4-mm, dark blue cyst on the surface of the tunica albuginea; the cyst excised and the defect in the tunica albuginea closed.

Case 5. A 50-year-old man was found to have an asymptomatic right testicular mass on routine physical examination. He reported a contusion injury to the testes when he was 18 years old. A non-tender, 5-mm mass was found in the posterior medial area of the testis separate from the epididymis. Ultrasound demonstrated a 5-mm anechoic lesion on the surface of the testis, typical of a cyst of the tunica albuginea (Fig. 1). No surgery was performed and no change in the cyst has been observed over 2 years.

Case 6. An asymptomatic left testicular mass was palpated in a 52-year-old man with extensive metastatic hepatocellular cancer. It lay on the lateral aspect of the testis and was not tender. Metastasis was suspected but ultrasound demonstrated a 5 mm × 6 mm anechoic lesion on the surface of the testis typical of a cyst of the tunica albuginea, and the testis was left alone. The patient later died of his malignant disease and the diagnosis was confirmed at autopsy.

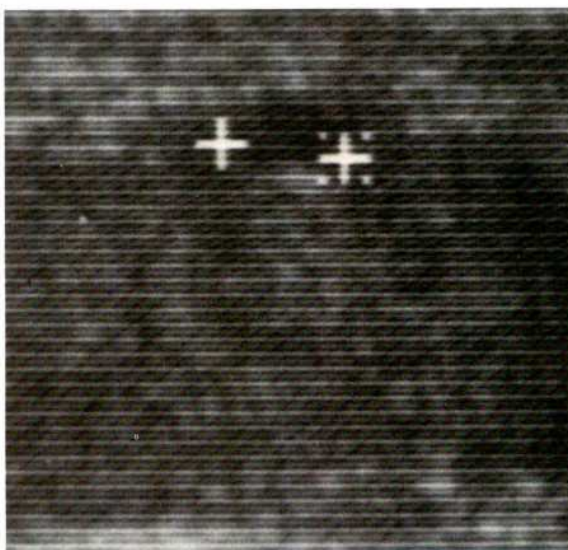


Fig. 1 Anechoic lesion on the surface of the testis (crosses)—a cyst of the tunica albuginea (case 6).

Histological findings

Light microscopic and immunohistochemical findings are summarised in Table 2. The columnar epithelium of the cyst contained cells with cilia in 2 cases (Nos. 2 and 4) (Fig. 2), while most of the cells were simple, without cilia. In 1 case (no. 1) the cyst was lined with a low cuboidal or flattened epithelium and no ciliated cells could be seen. This patient also had a small epithelial defect which contained histiocytic cells. In 1 case (no. 3) the epithelium resembled transitional epithelium (Fig. 3) and was composed of 1 to 6 layers. The uppermost layer was reminiscent of umbrella cells and contained PAS-positive, diastase-resistant material. The deeper cells had a clear cytoplasm and contained PAS-positive granules, which disappeared with diastase treatment.

Histochemical staining with Alcian blue at pH 1 and pH 2.5 showed faint positive staining at the apical surface of the cells lining the cysts and secreted material, except for case 4, which was negative. No secreted material was present in case 3. Staining was not affected by hyaluronidase. Apart from case 3, in all cases the cells contained a little PAS-positive material which was diastase resistant. The secreted material was similarly PAS-positive.

Discussion

The cysts were located in the tunica albuginea in our 4 surgical patients, as in previous reports (Frater, 1929; Arcadi, 1952; Mancilla-Jimenez and Matsuda, 1975; Turner *et al.*, 1977; Mennemeyer and Mason, 1979; Sethney and Albers, 1980; Warner *et al.*, 1984; Mevorach *et al.*, 1985; Bryant,

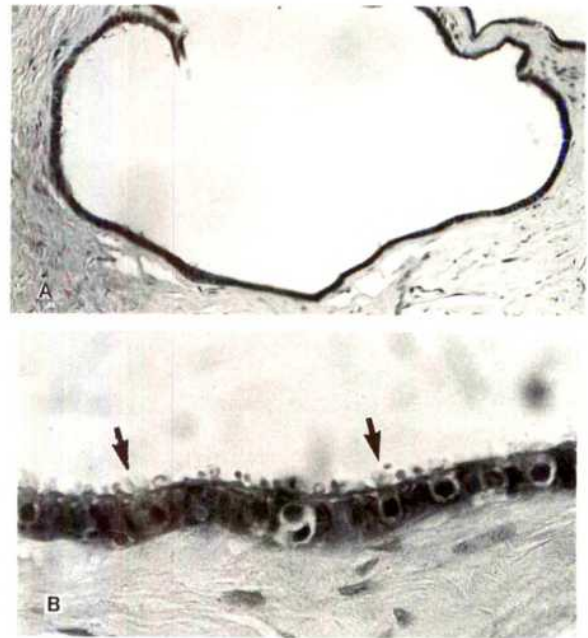


Fig. 2 (A) Light micrograph of cyst lined with columnar epithelium (case 2). (H and E $\times 106$). (B) Occasional cells with cilia are present (arrows). (H and E $\times 422$).

1986). Our surgical patients were about 20 years younger, however, than those in most of the earlier reports, in their 20s and 30s (Mancilla-Jimenez and Matsuda, 1975; Warner *et al.*, 1984). All had discovered the testicular masses themselves. Cysts may be asymptomatic and discovered incidentally (Mancilla-Jimenez and Matsuda, 1975; Mennemeyer and Mason, 1979; Bryant, 1986) or associated with testicular pain or swelling (Arcadi, 1952; Sethney and Albers, 1980). Three of our patients

Table 2 Histological Findings in Cysts of the Tunica Albuginea

Case no.	No. of cysts	Epithelium	Wall	Inflammation	Immunohistochemistry	
					Cytokeratin	CEA
1.	Single	Low cuboidal	Fibrotic, smooth muscle cells	None	—	+
2.	Multilocular	Low columnar with ciliated cells	Fibrotic	None	+	—
3.	Multilocular	Transitional-like	Fibrotic	None	+	+
4.	Multilocular	Low columnar with ciliated cells	Fibrotic	Occasional lymphocytes	—	+

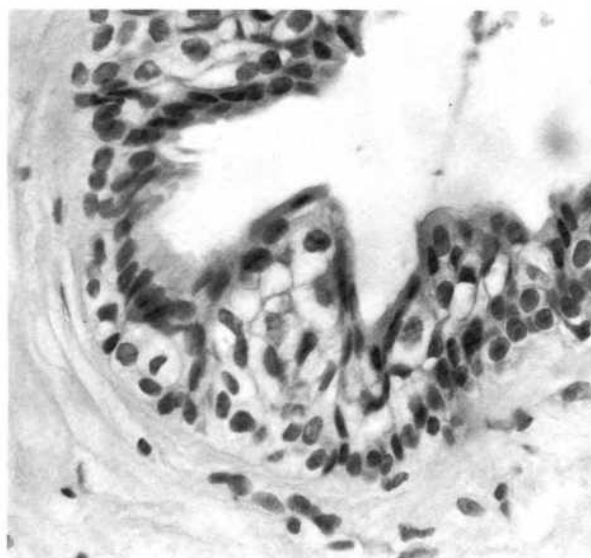


Fig. 3 Light micrograph of multilocular cyst lined with transitional-like epithelium (case 3). The thickness of the epithelium varies from 1 to several layers. (H and E $\times 422$).

also reported occasional testicular tenderness or pain. The cysts are usually small, solitary, multiple or multiloculated, and are commonly located on the anterior and lateral aspect of the testis (Mancilla-Jimenez and Matsuda, 1975). They seem to be found equally frequently in either testis and not predominantly in the right testis, as is observed in germ cell tumours (Arcadi, 1952; Mancilla-Jimenez and Matsuda, 1975; Mennemeyer and Mason, 1979; Sethney and Albers, 1980; Takihara *et al.*, 1982; Warner *et al.*, 1984; Malek *et al.*, 1985; Mevorach *et al.*, 1985; Bryant, 1986). The cysts usually contain serous fluid (Mancilla-Jimenez and Matsuda, 1975), but turbid fluid has also been reported, as in 2 of our patients (Mennemeyer and Mason, 1979).

The aetiology of the cysts is not known, but it has been postulated that trauma and subsequent haemorrhage into the tunica albuginea could lead to their formation (Frater, 1929). Arcadi (1952) favoured an infectious aetiology, since he found evidence of testicular inflammation in 2 of his cases. These theories have little relevance to our 6 patients, however, as their histories included only 1 genital trauma and no infections, and no evidence of inflammation was found at operation in the 4 surgical cases. Another theory is that they arise from embryonic remnants. This is supported by the finding of fibrous walls and glandular inclusions and their common location on the anterior and

lateral aspects of the testis (Mancilla-Jimenez and Matsuda, 1975; Warner *et al.*, 1984).

Mennemeyer and Mason (1979) confirmed the epithelial nature of the cysts by electron microscopy and suggested that they are of efferent duct origin, probably congenital, and enlarge over a period of years owing to accumulation of fluid or to haemorrhage. Bryant (1986) also found a few scattered cells with cilia on their luminal sides under a high-powered microscope, supporting an origin in the efferent ductules, which was also suggested by their location near these ductules. In 2 of our patients the epithelium contained ciliated cells. In 1 case no ciliated cells could be detected, but the cysts showed features suggestive of distension (a flattened epithelium and focal erosion of the epithelium), which could have destroyed the cilia. The histochemical features of the lining cells or secreted material did not differ from those of the other 2 cysts with ciliated cells, further supporting our interpretation that they are lined with the same type of epithelium. Thus the findings in 3 of our 4 cysts seem to support the concept of an epithelial origin as suggested by Mennemeyer and Mason (1979) and Bryant (1986). Mancilla-Jimenez and Matsuda (1975) demonstrated the presence of acid mucopolysaccharides in the secreted material on the basis of the Alcian blue positivity of that present in the glandular inclusions, suggesting a mesothelial cell origin rather than a müllerian or wolffian epithelial origin. One of our cases also involved secreted material that was stained with Alcian blue at pH 1 but was lined with an epithelium containing ciliated cells, which are not present in the mesothelium.

One of the cystic lesions (case 3) was clearly different from the others structurally, being lined by transitional-like epithelium. As far as we know, this type of cystic lesion has not been previously described in the tunica albuginea. A similar type of epithelium is occasionally present in the subserosal surfaces of ovaries, where it is referred to as a Walthard's cell nest and thought to represent transitional cell metaplasia of the peritoneal mesothelium. This type of epithelium may also form tumours in ovaries (Brenner's tumours). A comparable epithelium has also been found in femoral hernial sacs from males, at the epididymotesticular junction in 1 case (Sundarasivarao, 1953) and in subserosa of the epididymis (Hartz, 1947). In addition, 4 cases of an intrascrotal Brenner's tumour have been described, 1 of which was combined with an adenomatoid tumour (Walker and Mills, 1988). The origin of the transitional-like epithelium in these structures is unknown, but a mesothelial

origin, either from metaplasia of the mature mesothelium or from remains of a müllerian duct, has been suggested (Walker and Mills, 1988). Our case may represent a mesothelial inclusion which contains transitional metaplasia for unknown reasons.

Cysts of the tunica albuginea have been considered extremely rare in urological practice and, as in our cases 1–4, they have manifested themselves clinically in a way that has aroused suspicion of a testicular neoplasm (Arcadi, 1952; Mancilla-Jimenez and Matsuda, 1975; Mennemeyer and Mason, 1979; Sethney and Albers, 1980; Bryant, 1986). This has led to unnecessary surgical exploration. High-resolution ultrasound with high sensitivity and specificity has changed the situation, however (Valvo *et al.*, 1983; Mevorach *et al.*, 1985; Gooding *et al.*, 1987; Benson, 1988; Mattila, 1989), and surgery can often be avoided, as in cases 5 and 6.

Cysts of the tunica albuginea seem to be rarer than those within the testis, the incidence of which is reported to increase with age (8 to 10% in men over 60 years) (Frater, 1929; Leung *et al.*, 1984; Gooding *et al.*, 1987). In the present study, ultrasound revealed 2 cases of tunica albuginea cysts, an incidence of only 0.3%. Comparing tunica albuginea cysts and intratesticular cysts, the latter must be considered more ominous because of the germ cell malignancies they may harbour (Azzopardi *et al.*, 1961; Price, 1969), whereas tunica albuginea cysts seem always to be benign. They cannot always be distinguished by ultrasound from cysts of the tunica vaginalis, however, although the latter are bigger (Mattila, 1989).

It is concluded that cysts of the tunica albuginea are more common than has previously been thought. They can probably be of both epithelial and mesothelial origin. Their importance lies in the fact that a malignant process cannot be ruled out on clinical grounds. High-resolution ultrasound examination can now distinguish them from solid testicular tumours, however, and so unnecessary surgery can be avoided. If a change in the physical findings is suspected in the course of later examinations, a repeat ultrasound examination will offer objective information for purposes of comparison.

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Histology of Testicular Biopsies taken at Operation for Bilateral Maldescended Testes in Relation to Fertility in Adulthood

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Summary—A total of 91 boys underwent bilateral orchiopexy with testicular biopsy. The percentage of tubular transverse sections containing spermatogonia, the fertility index (FI) and the number of spermatogonia per tubular transverse section (S/T) were measured and expressed as a percentage of the minimum normal value (FI% and S/T%, respectively). The maximum and mean of the 2 FI% and S/T% values were noted for each patient.

At follow-up, testicular volume was measured in 73 men; 71 of these gave a blood sample for FSH and 67 provided specimens of semen for analysis. The maximum and the mean FI% and S/T% values of the patients were positively correlated to maximal sperm density and to volume of pair of testes and negatively correlated to serum FSH.

It seems reasonable to use these histological parameters as prognostic indices of fertility potential. In adulthood only 11 patients had sperm density ≥ 20 million/ml, 37 had normal serum FSH and 29 had bilateral testicular volume ≥ 15 ml.

Patients with both testes originally placed in the superficial inguinal pouch at surgical exploration had a higher maximal sperm density than the rest of the study group.

The number of spermatogonia per tubular transverse section (S/T) and the percentage of tubular transverse sections containing spermatogonia (the fertility index (FI)) have been used to quantify spermatogonia in normal and in maldescended testes. It is primarily on account of such studies that current opinion favours treatment of maldescended testes before 2 years of age (Scorer and Farrington, 1971; Hadziselimovic, 1981; Hedinger, 1982). It has been shown statistically that both the S/T and the FI are significantly positively correlated to the actual number of spermatogonia per testis in normal males (Cortes, 1990). The prognostic value of S/T and FI in respect of fertility potential remains to be established.

The state of both testes must be considered to influence later fertility, and evaluation of bilateral testicular biopsies therefore seems important. In 20

to 25% of patients who are surgically treated for maldescended testes, both testes are affected (Puri and O'Donnell, 1988; Thorup and Cortes, 1990).

We present a study of 91 patients who underwent bilateral orchiopexy with testicular biopsy. In adulthood, semen quality, serum FSH and testicular volume were examined. The results were related to the S/T and FI in the testicular biopsies as well as to the anatomical position of the testes at surgical exploration.

Patients and Methods

The study group comprised 91 patients who underwent bilateral orchiopexy with testicular biopsy between 1972 and 1981 and were older than 21 years at follow-up. The routine of the department was primary human chorionic gonadotrophin (HCG) treatment for maldescended testes, and 66 (73%) of the 91 patients had previously been treated

unsuccessfully with HCG. HCG treatment was sometimes omitted if the testes were suspected of being ectopic in the superficial inguinal pouch and the patient had reached puberty. One patient had unilateral anorchia. Further details of the patients and of the surgical techniques appear in a previously published study (Thorup *et al.*, 1984). Of the 91 patients, 81 (89%) underwent bilateral testicular biopsy, 2 biopsies were unsuccessful and 10 patients underwent unilateral testicular biopsy.

The specimens were fixed in Stieves fluid. Serial sections of 4 μ m were stained with haematoxylin and eosin and examined by light microscopy. The percentage of tubular transverse sections containing spermatogonia, the fertility index (FI) and the number of spermatogonia per tubular transverse section (S/T) were measured from 100 tubular transverse sections which were examined by systematic stepwise movements of the stage. The results were compared with previously published material of normal autopsy testes (Cortes, 1990). The normal values of FI and S/T depend on the age of the patient; therefore the FI and S/T were expressed as a percentage of minimum for the age and named FI% and S/T% respectively. For every patient the maximum and the mean of the 2 FI% and S/T% values were found and named FI% max, FI% mean, S/T% max and S/T% mean respectively.

The patients were divided into 3 histological groups according to the FI% and S/T%:

- (1) Bilaterally normal or mild histopathological changes only; the FI%/S/T% values were $\geq 95\%$ in both testicular biopsies.
- (2) Moderate histopathological changes.
- (3) Bilaterally severe histopathological changes including Sertoli-cell-only syndrome; the FI%/S/T% values were bilaterally $\leq 5\%$.

At follow-up the patients were sent a questionnaire requesting information about willingness to attend for examination. The questionnaire was returned by 87 (96%). One patient was subsequently excluded because Klinefelter's syndrome was recognised after the primary operations. Of the remaining group, 73 men (81%) agreed to undergo measurement of testicular volume with Prader's orchidometer (Prader, 1966); 71 of these men provided a blood sample for follicle-stimulating hormone (FSH) and 67 provided specimens of semen for analysis. Two specimens were offered by 52 men. Semen analysis was done according to standard techniques (WHO, 1987). For every patient the best sperm density in the samples of semen was termed maximal sperm density.

For statistical analysis the Mann-Whitney (M-W), Kruskal-Wallis (K-W) and Spearman rank correlation (Spearman) tests were used.

Results

In 68 patients there was an interval between the orchiopexies on the 2 sides (median 3 months, range 0–74, 25–75% percentiles 2–5 months). In every patient the mean age at operation was used in the statistical analyses. The median of the mean age at orchiopexy was 13.2 years (range 10.6–15.9, 25–75% percentiles 12.6–13.9 years). The median age at follow-up was 25.6 years (range 21.9–33.4).

The FI and S/T values for the 134 per-operative testicular biopsies of the patients who agreed to follow-up are shown in Figures 1 and 2 respectively, in relation to age at orchiopexy and to values in normal testes. In 8 biopsies (6%) both FI and S/T were normal; in addition, FI was normal in 3 biopsies and S/T was normal in 2 other biopsies. None of the 119 samples of semen from the 67 patients was normal according to WHO (1987) standards. Eleven patients (16%) had maximal sperm density ≥ 20 million/ml but the percentage of sperm with normal morphology was $< 50\%$ and/or the percentage of sperm without motility was $> 50\%$ (Table 1); 37 patients had maximal sperm density < 5 million/ml and 12 of these patients had azoospermia.

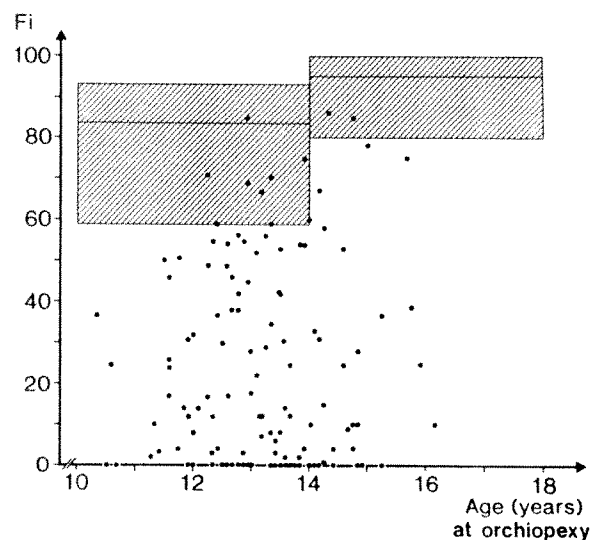


Fig. 1 Fertility index (FI) in 134 testicular biopsies at operation in 73 boys who underwent bilateral orchiopexy, compared with FI values in normal testes. Unbroken line, median; hatched area, range.

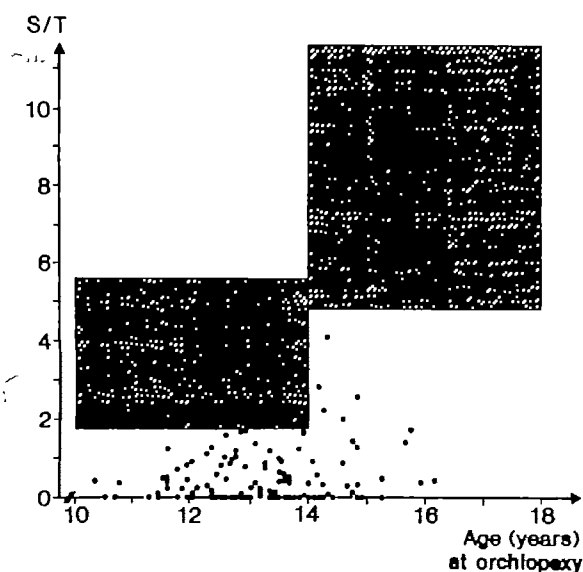


Fig. 2 Number of spermatogonia per tubular transverse section (S/T) in 134 testicular biopsies at operation in 73 boys who underwent bilateral orchiopexy, compared with S/T values in normal testes. Unbroken line, median, hatched area, range.

Each of the 4 parameters—FI% max, FI% mean, S/T% max and S/T% mean—was positively correlated to maximal sperm density (Spearman, $P < 0.001$).

Serum FSH was measured in 71 patients (95% reference percentiles 3–15 iu/l); no patient had values below the 2.5% percentile, while 34 patients (48%) had values above 15 iu/l and 11 of these had serum FSH > 30 iu/l. FI% max, FI% mean, S/T% max and S/T% mean in the per-operative testicular biopsies were negatively correlated to serum FSH in adulthood (Spearman, $P < 0.001$). Moreover, a negative correlation was found between serum FSH and maximal sperm density (Spearman, $P < 0.001$).

At follow-up in adulthood 131 testes (90%) were in a satisfactory scrotal position. Three patients had one of the testes in the superficial inguinal pouch and 10 patients had one testis in a high

scrotal position. In 11 of these cases the testis in the unsatisfactory position was smaller than the scrotal one, in 1 case by only 5 ml. Two patients had unilateral testicular atrophy (2 and 4 ml respectively) of a scrotal testis.

In only 29 patients (40%) was bilateral testicular volume ≥ 15 ml, which is normal according to Prader (1966). The median volume of pairs of testes was 27 ml (range 12–45). Each of FI% max, FI% mean, S/T% max and S/T% mean was positively correlated to the volume of pairs of testes in adulthood (Spearman, $P < 0.01$). In addition, total testicular volume was positively correlated to maximal sperm density (Spearman, $P < 0.01$) and negatively correlated to serum FSH (Spearman, $P < 0.01$).

In total, only 9 patients had normal maximal sperm density, serum FSH and volume of testes in adulthood.

The 41 patients in whom both testes were originally ectopic in the superficial inguinal pouch had a higher maximal sperm density (M–W, $P < 0.05$) than the other patients. It was not possible to demonstrate any difference in serum FSH (M–W, $P > 0.2$) or in volume of pairs of testes (M–W, $P > 0.08$) (Table 2).

A total of 69 patients (95%) were placed in the same histological group—A, B or C—by both the FI and S/T estimates. The follow-up results for the patients, according to the FI and S/T groups, appear in Tables 3 and 4 respectively.

There were no differences in age at orchiopexy (M–W, $P > 0.6$), FI% max (M–W, $P > 0.4$), FI% mean (M–W, $P > 0.1$), S/T% max (M–W, $P > 0.9$) or S/T% mean (M–W, $P > 0.6$) between the 73 patients who participated in the study and the 17 who did not.

Discussion

This study has demonstrated that the maximal and the mean of the age-correlated FI and S/T values—FI% max, FI% mean, S/T% max and S/T% mean—

Table 1 Results of Semen Analyses in 67 Men who underwent Bilateral Orchiopexy for Malescented Testes

	WHO standards	Median	(Range)
Volume (ml)	≥ 2	2.5	(0.7–6.0)
Max sperm density (million/ml)	≥ 20	4.1	(0.0–85.0)
Normal forms (%) ^a	≥ 50	24	(3–60)
Sperms without motility (%) ^a	< 50	50	(0–79)
Abstinence time (days)	2–7	3.5	(1–14)

^a 12 azoospermic.

Table 2 Results in 73 Patients who Underwent Bilateral Orchiopexy for Bilateral Maldescended Testes, according to Anatomical Location of the Testes at Surgical Exploration

	<i>No. of patients</i>	<i>Max. sperm density (million/ml)</i>	<i>Serum FSH (iu/l)</i>	<i>Volume of pair of testes (ml)</i>
Bilateral ectopic*	41	6.6‡ (0–85.0)	13.0§ (3.0–43.0)	30 (15–45)
Ectopic and ex ring†	11	0.6 (0–56.0)	22.0 (8.0–54.0)	24 (20–45)
Bilateral ex ring	9	1.5 (0–19.0)	10.8 (3.0–26.2)	27 (23–45)
Ectopic and canalicular	6	4.7** (0–20.0)	15.9 (7.0–30.0)	25 (18–35)
Ex ring and canalicular	3	0.9 (0–2.2)	26.0 (9.1–26.0)	18 (18–30)
Bilateral abdominal	1	0	25.0	17
Ectopic and abdominal	1	7.0	19.2	28
Ectopic and agenesis	1	0	25.0	12

Values are medians with ranges in parenthesis.

*Ectopic in the superficial inguinal pouch.

† At the external inguinal ring.

‡ 37 patients only.

§ 39 patients only.

** 4 patients only.

Table 3 Results in 73 Men who Underwent Bilateral Orchiopexy for Maldescended Testes, Divided into Groups FI-A, -B, -C according to the Histopathological Changes in the Bilateral Testicular Biopsies at Operation

	<i>Normal or mild changes A</i>	<i>Moderate changes B</i>	<i>Severe changes C</i>	<i>Kruskalla-Wallis test</i>
No. of patients	3 (4%)	50 (68%)	20 (27%)	
Age in years at orchiopexy	13.3 (12.5–14.9)	13.2 (10.6–15.9)	13.2 (10.7–15.5)	$P > 0.9$
Age in years at follow-up	26.7 (22.5–28.6)	25.8 (21.9–33.4)	24.1 (22.0–30.5)	$P > 0.6$
Max. sperm density (million/ml)	29.0 (24.0–44.0)	7.0* (0.03–85.0)	0.03† (0–12.0)	$P < 0.00001$
Serum FSH (iu/l)	13.8 (4.0–17.0)	10.3‡ (3.0–43.0)	25.5 (11.6–54.0)	$P < 0.0001$
Volume of pair of testes in adulthood (ml)	40 (22–45)	30 (15–45)	22 (12–35)	$P < 0.0005$

Values are medians with ranges in parentheses.

* 45 patients only.

† 19 patients only.

‡ 48 patients only.

correlated with subsequent sperm and serum FSH measurements. These may therefore indicate the fertility potential of boys with bilateral maldescended testes.

It must be emphasised that the degree of

histopathological changes in the biopsies of the individual patient did not strictly predict the degree of abnormalities in maximal sperm density, serum FSH and volume of pairs of testes in adulthood. This could be explained partly by an uneven

Table 4 Results in 73 Men who Underwent Bilateral Orchiopexy for Malescended Testes, Divided into Groups S/T-A, -B, -C according to the Histopathological Changes in the Bilateral Testicular Biopsies at Operation

	Normal or mild changes A	Moderate changes B	Severe changes C	Kruskalla- Wallis test
No. of patients	3 (4%)	47 (64%)	23 (32%)	
Age in years at orchiopexy	13.3 (12.5-14.9)	13.1 (10.6-15.9)	13.3 (10.7-15.5)	$P > 0.8$
Age in years at follow-up	26.7 (22.5-28.6)	25.7 (21.9-33.4)	24.2 (22.0-30.6)	$P > 0.9$
Max. sperm density (million/ml)	29.0 (24.0-44.0)	6.9* (0.03-85.0)	0.005† (0-34.0)	$P < 0.0001$
Serum FSH (iu/l)	13.8 (4.0-17.0)	10.5‡ (3.0-40.0)	25.0† (12-45)	$P < 0.001$
Volume of pair of testes in adulthood (ml)	40 (22-45)	30 (18-45)	24 (12-45)	$P < 0.005$

Values are medians with ranges in parentheses.

* 42 patients only.

† 22 patients only.

‡ 46 patients only.

distribution of spermatogonia in different parts of the tubules in malescended testes which has also been described in children (Knecht, 1976). Another explanation may be impaired spermatogenesis in adulthood: for example, spermatogenic arrest and reduced number of spermatids, which have been described in the majority of men previously treated for malescended testes (Giwerzman *et al.*, 1989). Retention of the spermatozoa may also be a factor. This may be caused by obstruction at the level of the epididymo-testicular fusion, the epididymis, the vas deferens or the ejaculatory duct—either congenital or caused by per-operative surgical lesions, or infections. Macroscopic abnormalities of the epididymis have been reported with incidences ranging from 1.2 to 36% in patients with malescended testes (Dean *et al.*, 1952; Marshall and Shermeta, 1979; Heath *et al.*, 1984). One of our patients had azoospermia, normal serum FSH and testicular volumes of 15 and 12 ml, which theoretically indicates bilateral obstruction. Finally, testicular atrophy caused by surgical lesions may exist; in 2 of our patients such unilateral atrophy was suspected. The reported incidence of post-operative atrophy is 1 to 28% (Fahlström *et al.*, 1963; Gross and Replogle, 1963). The FI% mean and S/T% mean were as good as the FI% max and S/T% max as prognostic indices, although it might be expected theoretically that the maximal number of spermatogonia in the 2 testicular biopsies would be most

predictive of future fertility. However, it has been proposed by Hadziselimovic *et al.* (1984) that the same pathological condition may exist in both testes.

The study has also demonstrated that the histopathological groups A, B and C had some prognostic value. Patients with normal findings or mild histopathological changes only (group A) had better semen findings. Patients with severe histopathological changes (group C) had poor semen analyses. In group B the fertility potential was more unpredictable because the FI% max, FI% mean, S/T max and S/T% means respectively were not well correlated to maximal sperm density.

In evaluating semen we used the WHO (1987) criteria. A sperm density ≥ 20 million/ml was regarded as normal. Some authors have suggested 5 million/ml as the lowest normal value (Smith *et al.*, 1977). In contrast to previous studies we used the best sample of semen because marked variation in sperm output may occur within 1 individual (WHO, 1987). In spite of this we found only 16% of the patients (95% confidence limits 8.5-27.5%) with sperm density ≥ 20 million/ml, which is probably a lower value than the 25% of patients with sperm density ≥ 20 million/ml that emerges from combining previously published results of patients treated for bilateral malescended testes (Chilvers *et al.*, 1986; Puri and O'Donnell, 1988). In most of these studies the patients were not initially treated with

HCG. It has been suggested that a successful response to HCG distinguishes the superior testes with a better prognosis (Richer *et al.*, 1976; Bierich, 1981; Spitz, 1983). In 7 previously published investigations, including 126 patients in total, the majority had pre-operatively undergone unsuccessful treatment with HCG, as did our patients. In combining the results of these reports, 17% of the patients had a sperm density ≥ 20 million/ml in adulthood, which is in accordance with our figure (Hohenfeller and Eisenhut, 1964; Hortling *et al.*, 1967; Richter *et al.*, 1976; Werder *et al.*, 1976; Albescu, 1979; Schreiber *et al.*, 1981; Hadziselimovic *et al.*, 1984).

The patients whose testes were originally ectopic in the superficial inguinal pouch had a higher maximal sperm density than the rest of the patients, but the median maximal sperm density was only 6.6 million/ml and only 20% had maximal sperm density ≥ 20 million/ml. We therefore neither support Bramble *et al.* (1974), who found that the site of the testes at surgical exploration did not affect fertility, nor Puri and O'Donnell (1988), who found that the patients surgically treated for bilateral maldescended testes in the superficial inguinal pouch produced normal or acceptable semen. Both studies, however, included only 23 patients, and the patients were not pre-operatively treated unsuccessfully with HCG. Moreover, the patients were a little younger at orchiopexy than our patients (mean 11.5 and 9.7 years respectively). This might influence the results.

The negative correlation between serum FSH and maximal sperm density confirms previous findings (Kjessler and Wide, 1973; Bramble *et al.*, 1974; Hadziselimovic *et al.*, 1984). Normal basal serum FSH and maximal sperm density ≥ 20 million/ml were found in 15% of our patients (95% confidence limits 7.6–26.5%). This is in accordance with 1 of 6 patients who were also treated unsuccessfully with HCG before operation (Hadziselimovic *et al.*, 1984), but probably lower than 10 of 21 patients who were not selected according to HCG treatment (Bramble *et al.*, 1974). Partial obstruction of the spermatozoa or partial pituitary failure may be suspected in 18% of our patients (95% confidence limits 9.9–30%) who had normal serum FSH and a maximal sperm density < 5 million/ml (Kjessler and Wide, 1973). In both of the above studies the corresponding figures were 17% if the patients were treated unsuccessfully with HCG (Hadziselimovic *et al.*, 1984) and 9.5% if they were not selected according to HCG treatment (Bramble *et al.*, 1974). In some boys with maldes-

cended testes, impairment of the hypothalamo-pituitary-gonadal axis has been found (Job *et al.*, 1977; Bierich, 1981; Hadziselimovic, 1981; Spitz, 1983). Treatment of maldescended testes with HCG or luteinising hormone-releasing hormone (LH-RH) is based on these findings. In none of our patients was there evidence of Kallman's syndrome (pituitary hypogonadism).

Although the volume of pairs of testes in adulthood was positively correlated to the maximal sperm density and negatively correlated to serum FSH, we do not fully agree with the opinion that testicular volume in adulthood is a reliable index of reproductive function (Werder *et al.*, 1976). A normal macroscopic appearance of both testes was found in only 35% of patients having a maximal sperm density ≥ 20 million/ml and normal serum FSH, but a considerable decrease in total testicular volume to ≤ 20 ml was found in 12 of the 13 patients with a maximal sperm density < 10 million/ml and elevated serum FSH.

There was agreement with reports on the macroscopic results at follow-up (Scorer and Farrington, 1971; Bramble *et al.*, 1974; Werder *et al.*, 1976; Hadziselimovic *et al.*, 1984; Chilvers *et al.*, 1986).

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Surgery Following Chemotherapy for Metastatic Testicular Teratoma

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Summary—Twenty patients with metastatic testicular teratoma underwent surgery for residual disease after chemotherapy. Twelve patients in whom complete excision of all residual masses was possible are alive with no evidence of disease. Four patients have died of malignant teratoma, 2 have active malignant disease and 2 have inoperable residual cystic disease.

Patients with malignant teratoma intermediate (MTI) primary testis tumours, and those with bulky abdominal disease at presentation, are more likely to have residual masses requiring excision. Completeness of excision appears to be the most important predictor of disease-free survival.

The results of treatment for metastatic germ cell tumours have improved dramatically since the introduction of cisplatin, with the majority of patients now achieving both a complete response and long-term survival (Ellis and Sikora, 1987).

In some patients, however, nodal or pulmonary metastases may only partly regress or even increase in size while serum tumour markers fall (Logothetis *et al.*, 1982). Failure to achieve a complete response in other malignant tumours that are curable by chemotherapy usually implies a bad prognosis, but this is not necessarily the case with metastatic testicular teratoma. Residual masses in the presence of normal markers may not be malignant, but represent either mature (differentiated) teratoma, fibrous or necrotic tissue (Tait *et al.*, 1984). As there is no non-invasive technique for distinguishing residual malignant from non-malignant tissue, it is now common practice to excise residual masses after chemotherapy, for diagnostic and therapeutic purposes.

We report the results in 20 patients with metastatic testicular teratoma, where residual or recurrent masses were excised after completion of chemotherapy.

Patients and Methods

Between January 1978 and March 1989, 96 consecutive patients with advanced testicular teratoma were treated with cisplatin-based chemotherapy. From 1975 to 1983, patients received cisplatin, vinblastine and bleomycin, and since 1983 etoposide has been substituted for vinblastine. Details of these treatments and results have been reported previously (Taylor *et al.*, 1985; Coleman *et al.*, 1991). Sixty-one patients (64%) achieved a complete radiological and tumour marker response (CR). Forty-three (45%) have subsequently required 1 or more additional treatments, including 7 who relapsed after achieving a CR.

Twenty patients with a median age of 29 years (range 14–50) have undergone surgical excision for residual (n=16) or recurrent (n=4) metastatic disease. Sixteen have had 1 operation, 3 have required a second operation and 1 a third. Seventeen patients had abdominopelvic lymph nodes removed, 4 had supraclavicular lymph nodes excised and in 4 cases pulmonary metastases were removed. Multiple sites were treated in 5 patients. Our policy has been to excise any residual disease that can be detected by physical examination or currently available imaging techniques, including computed tomography (CT), providing the serum tumour

markers alpha fetoprotein (AFP) and β human chorionic gonadotrophin (β -HCG) are normal or near-normal. In the abdomen we have attempted to excise completely any area with residual enlarged lymph nodes, but have not performed a bilateral radical retroperitoneal lymphadenectomy in every case.

The median time from surgery was 45 months (range 2–82) and no patient has been lost to follow-up. There have been no post-operative deaths. All histology has been reviewed by a single pathologist (A.M.L.).

Results

Complete excision of all disease was possible in 12/20 patients, including 1 who required a second laparotomy for total clearance. All 12 patients are alive and well with no evidence of disease (Fig.). The histology of the excised masses from these 12 patients revealed differentiated teratoma in 7 cases and necrotic tissue only in 3. One patient had what was classified as MTI, although this was predominantly differentiated disease with only 1 microscopic focus of malignant tissue and a raised serum AFP. The twelfth patient had MTI with a significant malignant component. Neither of these last 2 cases received post-operative chemotherapy and both remain disease-free 72 and 12 months from surgery respectively.

Eight patients had incomplete excisions. Three had unsuccessful thoracotomies with tumour adherent to pleural or mediastinal structures. In 4 patients with unsuccessful abdominopelvic operations the removal of residual involved lymph nodes was

thought to be too hazardous. The eighth patient had extensive matted tumour adherent to the posterior abdominal wall and biopsy was all that was technically possible.

In 3 patients the resected mass was malignant. In 2 cases this was classed as malignant teratoma undifferentiated (MTU), death occurring within 3 months of surgery. The third patient had MTI and died 9 months after excision. In all 3 cases serum tumour markers were elevated at the time of surgery. In the other 5 patients who had incomplete excision, the resected masses showed the features of differentiated teratoma. One of these, the patient with extensive tumour adherent to the posterior abdominal wall, died 3 months after surgery despite further chemotherapy. Although the other 4 are alive, 2 have recently suffered a late relapse with rising AFP 55 and 72 months following surgery. The other 2 have had radiotherapy (1 abdominal, 1 mediastinal) in an effort to achieve local control. Both have residual masses and in the patient with mediastinal disease the masses continue to grow.

Tumour characteristics which predicted patients who were likely to need post-chemotherapy surgery were histological subtype (Table 1) and tumour bulk (Table 2); 11/25 patients (44%) with metastases from malignant teratoma intermediate tumours required surgery compared with 6/64 (9%) with undifferentiated disease ($P=0.00067$); 71 of the original 96 patients had abdominal lymph nodes at presentation. The CR rate for patients with bulky abdominal disease (>5 cm transverse diameter) was less than that achieved in non-bulky disease and surgery or other treatments were required more frequently ($P=<0.05$).

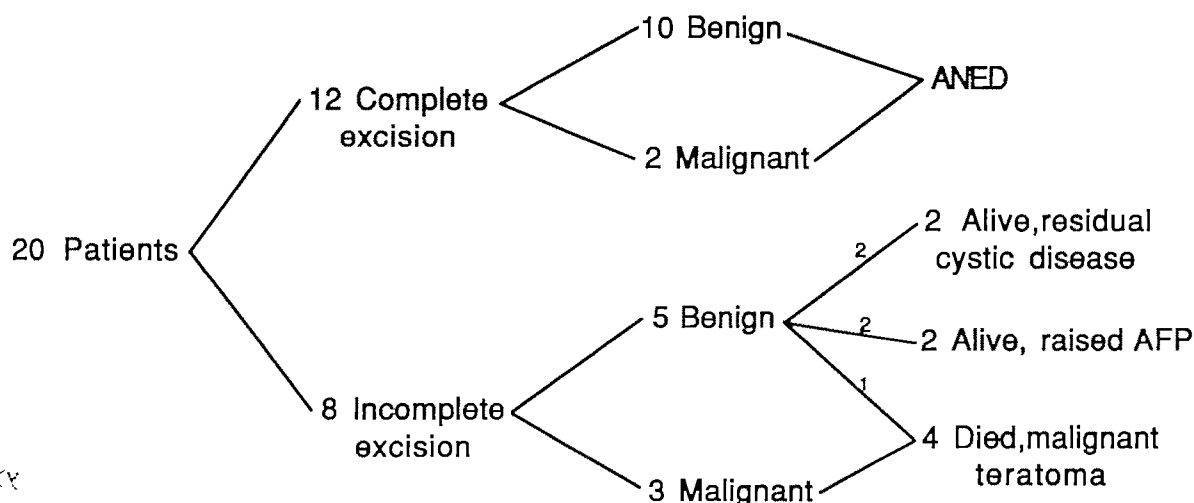


Fig. Outcome according to completeness of excision

Table 1 Subsequent Treatment Required According to Testis Histology

Testis histology	Complete response	Residual masses excised	Progressive disease requiring radiotherapy or chemotherapy	Total
MTI	12	11	2	25
MTU	45	6	13	64
Total	57	17	15	89

$$\chi^2_{(2)} = 14.61 \quad P = 0.00067$$

Discussion

We have found that complete excision of residual masses following chemotherapy for testicular teratoma is important for long-term survival and this confirms results from other centres (Tait *et al.*, 1984; Loehrer *et al.*, 1986). Although our experience is small, it may also be possible surgically to salvage patients with malignant disease in the resection specimen, providing complete clearance can be achieved.

The prognosis, however, of patients in whom only partial excision is possible is relatively poor, particularly in those with incompletely resected malignant disease. All 3 of these patients have died. Three of 5 with partially resected benign disease have subsequently developed malignant disease which has proved refractory to further chemotherapy. One of these has died and the other 2 are alive with raised serum AFP. Sampling errors may lead to an erroneous diagnosis of differentiated teratoma or necrosis, leaving behind malignant disease. The patient who died following incompletely resected disease is probably an example of this. Death from malignant teratoma occurred 3 months after laparotomy, when a biopsy only was possible, although the biopsy showed differentiated teratoma only.

This could also account for the relapses after partial excision in the other 2 patients, although the long time to relapse suggests transformation of differentiated disease to malignant teratoma as a more plausible explanation.

Patients with raised markers at the time of surgery have a poor prognosis and at present we do not favour routine operation in this group. Although our surgical experience in this situation is small, others agree with this approach (Ewing *et al.*, 1987). One exception, however, may be those patients with resectable disease confined to the abdomen (Williams *et al.*, 1989).

The source of differentiated teratoma in metastatic deposits is not entirely clear. It is unlikely that chemotherapy induces differentiation of malignant histology to mature teratoma (Oosterhuis *et al.*, 1983) and selective destruction of components other than mature teratoma is more probable. The histological subtype MTI contains differentiated elements which can be found in both the primary tumour and untreated metastases (Collins and Pugh, 1964; Oosterhuis *et al.*, 1983). Both our findings and those of others (Tait *et al.*, 1984; Loehrer *et al.*, 1986) of a higher frequency of residual masses in patients with MTI histology support this hypothesis.

It is concluded that patients with MTI primary tumours and those with bulky disease at presentation are more likely to have residual masses after chemotherapy which require additional treatment. If the tumour markers are normal these masses should be completely excised, and if this is possible the prognosis is good (Hendry *et al.*, 1987) even when the resection specimen contains malignant elements. If resection is incomplete, additional treatment is probably necessary. Repeat operation by a specialist surgeon, radiotherapy or chemotherapy should be considered, the choice depending on the site, extent and histology of the residual disease.

Table 2 Subsequent Treatment Required to Abdominal Lymph Nodes According to Initial Size of Nodes

Abdominal node size	Complete response, no further therapy	Residual mass requiring excision	Progressive disease requiring radiotherapy or chemotherapy	Total
< 2 cm	20	5	5	30
2-5 cm	10	3	3	16
> 5 cm	7	9	9	25
Total	37	17	17	71

$$\chi^2_{(4)} = 9.56 \quad P < 0.05$$

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Low Dose Bleomycin with Etoposide and Cisplatin for Metastatic Testicular Teratoma

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Summary—Thirty-nine men with metastatic testicular teratoma were treated with a combination of bleomycin, etoposide and cisplatin (BEP). Unlike the usual regimen of these 3 agents, bleomycin and cisplatin were given on day 1 only of the cycle, with etoposide for 3 days. Thirty patients (77%) are alive and disease-free after a median follow-up of 31 months—24/25 (96%) with disease confined to lymph nodes but only 6/14 (43%) patients with lung involvement.

Modified BEP chemotherapy is a well tolerated alternative to standard BEP chemotherapy for small volume nodal disease; it minimises in-patient time, hospital visits and the risk of bleomycin lung toxicity. However, omission of the weekly doses of bleomycin and shortening of the administration schedule of cisplatin and etoposide may be detrimental in patients with more extensive disease, for whom more intensive therapy may be necessary.

The prognosis of metastatic testicular teratoma has improved dramatically during the last 15 years with the development of platinum-based chemotherapy (Einhorn and Donohue, 1977). Recent refinements have been aimed at reducing the toxicity, duration and complexity of treatment in patients with a good prognosis (Horwich *et al.*, 1989) and improving the results in those with a poor prognosis by intensifying treatment and the addition of new active agents (Loehrer *et al.*, 1985; Kaye *et al.*, 1989).

The combination of bleomycin, etoposide and cisplatin is widely used for the treatment of metastatic germ cell disease. Each treatment is usually given over 5 days on an in-patient basis and weekly hospital visits are necessary for the administration of bleomycin. The importance of bleomycin in treatment is uncertain (Peckham *et al.*, 1985; Brada *et al.*, 1987). Proof of single agent activity is limited and lung toxicity a well recognised and occasionally fatal event. Because of this dilemma a randomised trial of BEP versus etoposide and platinum (EP) was instituted by the EORTC. Preliminary results suggest that BEP and EP are

equivalent (Stoter *et al.*, 1987) but the final results are still awaited.

For the last 6 years a modified BEP regimen has been used in Edinburgh with cisplatin administered on day 1 only and the usual day 9 and 16 doses of bleomycin omitted. This approach was developed from a similar modification of the Einhorn regimen (Taylor *et al.*, 1985) with the aim of reducing in-patient time, out-patient visits and the risk of bleomycin lung damage.

Patients and Methods

Between January 1983 and January 1989, 60 men either presented to the Western General Hospital with, or developed on surveillance, metastatic testicular teratoma requiring chemotherapy; 39 were treated with the modified BEP regimen and form the basis of this report.

Patients were staged by clinical examination, chest X-ray and computed tomography (CT) of the chest and abdomen according to the Royal Marsden Hospital classification (Peckham *et al.*, 1979). Measurement of the serum tumour markers alpha-fetoprotein (α FP) and beta-human chorionic gonadotrophin (β HCG) was performed before treatment

and repeated regularly during both treatment and follow-up after chemotherapy; 30 patients had raised tumour marker(s) at the start of chemotherapy.

Tumour staging, bulk of disease, histological subtypes and tumour marker levels are shown in Table 1. Eight patients had poor prognostic features (Medical Research Council, 1985); 6 had bulky disease (> 5 cm), 4 had β HCG levels > 1000 iu/l (3 of these with bulky disease) and 1 with α FP > 500 iu/l. In all patients the testis was considered to be the primary site of disease. There were no patients with liver or brain metastases. Fourteen patients had lung involvement but in the remaining 25 the disease was confined to the lymph nodes.

Table 1 Details of Patients

		No. of patients
Stage	IM	3
	IIA	13
	IIB	6
	IIC	2
	IIIA	1
	IVAL1	2
	IVBL1	2
	IVAL2	6
	IVCL2	1
	IVAL3	1
	IVCL3	2
Histology*	MTU	17
	MTU + S	12
	MTI	10
α FP (iu/l)	Normal (< 6)	16
	6-50	11
	51-500	11
	> 500	1
β HCG (iu/l)	Normal (6)	24
	6-1000	11
	> 1000	4
	> 1000	5
LDH (u/l)	Normal (< 300)	9
	300-1000	21
	> 1000	5
	Not known	4

* MTU = malignant teratoma undifferentiated, MTI = malignant teratoma intermediate, S = seminoma.

Patients received 4 courses of chemotherapy every 3 weeks using a combination of bleomycin, etoposide and cisplatin. It has been our policy to give 2 courses of chemotherapy after achieving a complete remission. Therefore 7 patients, 5 with bulky disease and 2 who failed to achieve a complete remission, received an additional 2 courses of chemotherapy.

Each course of chemotherapy was administered as follows: bleomycin (30 mg) was given in 50 ml normal saline intravenously over 15 min on day 1. Etoposide (120 mg/m²) was administered in 500 ml normal saline intravenously over 1 h on days 1, 2 and 3. Each single dose of etoposide was not restricted to a maximum of 200 mg as in some previous studies (Brada *et al.*, 1987). Cisplatin (100 mg/m²) was infused in 500 ml of 10% mannitol over 1 h on day 1, following intravenous hydration with at least 1 l normal saline and followed by a further litre of intravenous fluid. For each course an admission to hospital was necessary for 2 nights only. Treatment was usually delayed if the white blood cell count was < 3.0 $\times 10^9$ /l or the platelet count < 100 $\times 10^9$ /l but this proved to be necessary in fewer than 10% of courses. Before each course of chemotherapy a 24-h urine collection was performed to ensure adequate renal function with a creatinine clearance > 60 ml/min.

Three patients developed clinically significant hearing loss and tinnitus, and carboplatin (400 mg/m²) was substituted for cisplatin. The anti-emetic policy varied slightly during the period of study but the most commonly used regimen was high dose metoclopramide with or without dexamethasone (Allan *et al.*, 1984).

After completion of chemotherapy all patients had follow-up CT scans to document response. Patients were reviewed monthly for the first year with a chest X-ray, and tumour markers and CT scans were repeated at intervals of 3 to 6 months for 2 years. The median duration of follow-up was 31 months (range 11-76).

Results

A total of 27 patients (69%) achieved a complete radiological remission of disease and 27/30 (90%) with elevated tumour markers before treatment had a complete marker response (Table 2). Four patients relapsed after achieving a complete remission; 1 is alive and currently disease-free after radiotherapy to an enlarging mass of para-aortic lymph nodes, 1 is alive but with active drug-resistant disease, and 2 have died (including 1 who defaulted during treatment). This latter patient refused treatment after 2 courses and defaulted from follow-up until symptomatic relapse occurred. He was re-treated with the same drugs, defaulted again, and recently treated a third time, but died despite achieving a partial remission.

Of 8 patients with a partial radiological response, 3 remain free from progression more than 2 years

Table 2 Response to Treatment with Modified BEP Chemotherapy

	<i>No. of patients</i>
Radiological response	
Complete response	27
Partial response	8
No change	1
Progressive disease	3
Tumour marker response	
Markers returning to normal	27
Markers remaining elevated	3
Marker negative throughout	9

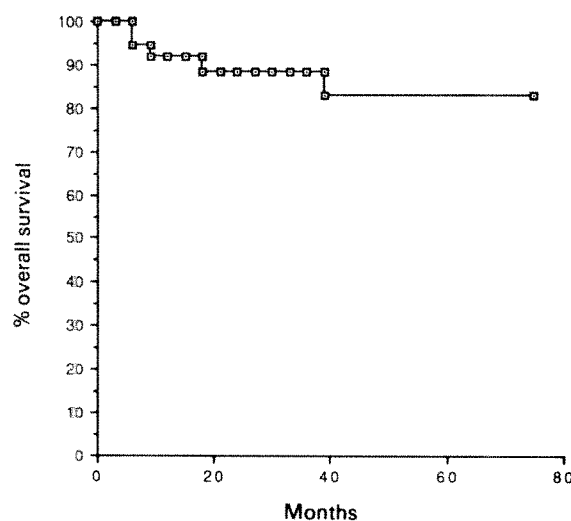
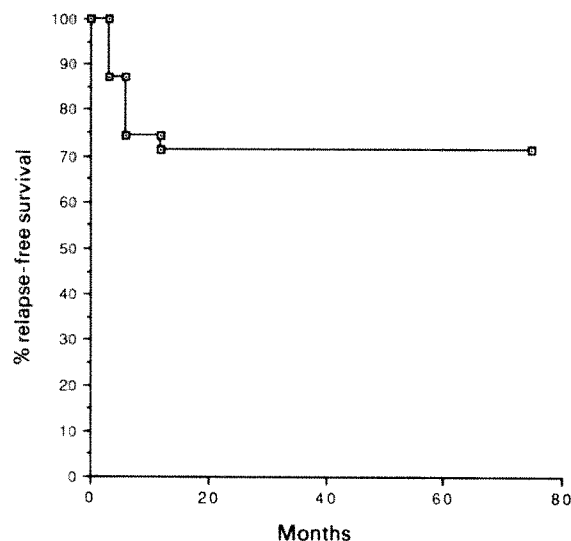
after chemotherapy with stable radiological abnormalities. In 4 patients the disease failed to respond on radiological investigations (no change or progressive disease) but in 3 the tumour markers returned to normal and surgical excision of disease revealed only differentiated teratoma.

Six of 12 patients with residual radiological abnormalities after chemotherapy, proceeded to surgery. Undifferentiated teratoma was found in 2 and mature, differentiated teratoma in 4. One patient with undifferentiated tumour in the operative specimen has died with recurrent disease. Seven patients have received chemotherapy on relapse. Transient responses have occurred but effective salvage chemotherapy has not been possible.

Thirty-two patients (82%) are alive and 7 have died with progressive drug-resistant disease (Fig. 1); 28 patients (72%) are relapse-free (Fig. 2). Two other patients are currently disease-free, having been salvaged by other modalities (1 with a residual para-aortic mass containing viable undifferentiated teratoma which was removed and another who recently received radiotherapy for a recurrent para-aortic mass). Neither of these patients had received additional chemotherapy. Two patients are alive but with active drug-resistant metastatic disease, having progressed after several chemotherapy regimes, and are expected to die.

Chemotherapy appears to have been curative in 24/31 good-risk patients (77%) and 4/8 (50%) with poor prognostic features; 24/25 patients (96%) with disease confined to lymph nodes are alive and currently disease-free compared with only 6/14 patients (43%) with lung involvement, 0/4 L1, 4/7 L2 and 1/3 L3 disease ($\chi^2 = 11.3$, $P < 0.001$).

The prognostic features of the 11 patients who have either died ($n = 7$), are alive with resistant

**Fig. 1** Overall survival after BEP chemotherapy.**Fig. 2** Relapse-free survival after BEP chemotherapy.

disease ($n = 2$), or are alive and disease-free after salvage therapy ($n = 2$) are shown in Table 3. Three had bulky disease and 1 an α FP > 500 iu/l, but in the remaining 7 there were no features to suggest a poor prognosis.

All patients were assessable for toxicity. There were no treatment-related deaths and no septicaemic episodes. High-tone deafness and tinnitus developed in 3 patients. None developed symptomatic lung toxicity.

Table 3 Prognostic Features at Presentation in Patients who have either Died, are Alive with Disease or Required Salvage Therapy

Stage	Disease volume*	α FP	β HCG	LDH	Disease state
IIA	S	315	28	384	Died
IVAL1	S	9	3	380	Died
IVAL1	S	51	3	245	Died
IVBL1	S	5400	3	538	Died
IVAL2	S	2	3	494	Died
IVBL1	S	2	3	1442	Died
IVAL3	VLV	2	6	5595	Died
IVAL2	S	11	3	302	Alive with disease
IVCL3	VLV	32	5103	3120	Alive with disease
IIA	S	2	490	286	Disease-free after XRT
IIC	LV	213	2000	757	Disease-free after surgery

* Small volume disease (S) includes stages IM, IIA, IIB, IIIA, IIIB, IVAL1, IVAL2, IVBL1, IVBL2, large volume (LV) disease includes stages IIC, IIIC, IVCL1, IVCL2 and very large volume (VLV) L3 disease.

Discussion

Cisplatin (or possibly carboplatin) is an essential component of any regimen for testicular tumours and minimum cumulative dose of 360 mg/m² has been suggested as necessary, particularly in the poorer prognostic groups (Newlands *et al.*, 1983). In most centres etoposide is now part of first-line chemotherapy. Its activity in germ cell malignancies is undoubted (Fitzharris *et al.*, 1980) and a randomised comparison of bleomycin, etoposide and cisplatin (BEP) versus bleomycin, vinblastine and cisplatin (PVB) showed slightly superior results with BEP, significantly less myelosuppression and fewer neuromuscular complications (Williams *et al.*, 1987).

Because bleomycin can cause pulmonary toxicity, which is occasionally fatal, several centres have investigated the possibility of omitting this agent. In patients with a good prognosis the 2-drug combination of etoposide and cisplatin (EP) appears to be equivalent to both the PVB (Bosl *et al.*, 1988) and the BEP regimes (Stoter *et al.*, 1987), producing a complete response in more than 90% of patients. However, in more advanced disease the contribution of bleomycin may be important. A small study performed at the Royal Marsden

† Hospital suggested that omission of bleomycin compromised the therapeutic results of treatment (Peckham *et al.*, 1985) and another from the same

centre concluded that weekly administration was necessary, particularly in patients with stage IV or bulky disease (Brada *et al.*, 1987).

In this non-randomised study our modification of the BEP regimen eradicated all malignant disease in 28/39 patients (72%). Treatment was well tolerated and there were no episodes of pulmonary toxicity. In patients with small volume nodal disease this regimen is a reliable alternative to the standard BEP regimen. The disease-free survival rate is 96%, similar to the results seen in most of the large centres (Williams *et al.*, 1987; Bosl *et al.*, 1988), with the advantage of a reduction in in-patient time and the number of out-patient visits.

However, the modified regimen was unsuccessful in controlling disease in 9/16 patients (56%) with advanced disease, either bulky nodal disease or parenchymal lung metastases, including 6 with none of the features generally recognised as conferring a worse prognosis and who would have been eligible for the EORTC study of EP versus BEP in low volume disease. In these patients omission of the usual weekly doses of bleomycin would appear to have been detrimental.

Alternatively, it may be that shortening the schedule of cisplatin or etoposide administration compromised the results of treatment. Most centres administer cisplatin over 3 to 5 days, although there is no evidence that this is necessary. Cisplatin is administered as a single infusion in the POMB-ACE combination and the published results with this treatment are at least as good as those with any other regimen (Newlands *et al.* 1986; Cullen *et al.*, 1988). In a recent report of a 24-h regimen of platinum, vinblastine and etoposide a 92% continuous complete remission rate was achieved (Wilkinson *et al.*, 1989). The efficacy of etoposide is known to be significantly affected by the schedule of administration (Slevin *et al.*, 1988) but whether a change from administration on days 1, 3 and 5 to days 1, 2 and 3 is important is not known.

Although the reduction of both toxicity and the use of medical resources is important, curative therapy remains the principal aim. Modification of established successful therapy in this and other curable malignancies is potentially hazardous and probably best attempted in the context of randomised clinical trials.

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Imaging Properties of Polydioxanone and Titanium Ligating Clips following Para-aortic Lymphadenectomy for Testicular Cancer

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Summary—Stainless steel ligating clips produce serious artefacts on CT scans. Polydioxanone (PDS) and titanium ligating clips were used in 15 patients during para-aortic lymphadenectomy for residual metastatic testicular teratoma following chemotherapy, and follow-up CT images were compared with those following the use of stainless steel ligating clips. PDS ligating clips did not produce any artefacts and were progressively absorbed. Titanium ligating clips produced artefacts similar to but less intense than those of stainless steel. PDS ligating clips should be used when follow-up CT scanning is important.

Ligating clips facilitate bloodless surgical dissection and are valuable in radical cancer surgery when division of numerous lymphatic as well as vascular channels may predispose to the development of lymphocele.

Following platinum-based chemotherapy for patients with metastatic non-seminomatous germ cell tumours (NSGCT), retroperitoneal lymphadenectomy is done for residual para-aortic masses demonstrable on computed tomography (CT) (Hendry *et al.*, 1987).

Stainless steel ligating clips are routinely used during this operation but we have been frustrated by the resultant artefacts that they cause on follow-up CT scans (Fig. 1). This problem is well recognised and relevant not only to uro-oncology but also to surgical oncology in general.

Ligating clips made from alternative materials, including titanium and the synthetic polymer polydioxanone (PDS), have recently become available. These materials are reported to cause less interference on CT scans *in vitro* (Weese *et al.*, 1984; Gross *et al.*, 1985). The purpose of the present study was to assess in patients undergoing post-

chemotherapy retroperitoneal lymphadenectomy for metastatic NSGCT the use and effect on post-operative CT images of ligating clips made from PDS and titanium.

Patients and Methods

In 10 consecutive patients with metastatic NSGCT, multiple PDS ligating clips (Absolok, Ethicon Ltd) were employed during retroperitoneal lymphadenectomy for post-chemotherapy residual masses. Post-chemotherapy abdominal and thoracic CT scans were performed in the pre-operative period and repeated in the early (2–4 weeks) and later (3–6 months) post-operative periods. In 5 further patients multiple titanium ligating clips (Premium Surgiclip, Autosuture) were used and post-operative CT scans performed at 1 month. The operative use and post-surgical CT appearances of these 2 different types of ligacip were compared with each other and with our previous experience of stainless steel ligating clips in over 100 patients undergoing retroperitoneal lymphadenectomy (Hendry *et al.*, 1987).

Results

No complications related to the use of either type of ligating clip were encountered.

† Based on a Poster Demonstration at the 46th Annual Meeting of the British Association of Urological Surgeons in Scarborough, July 1990

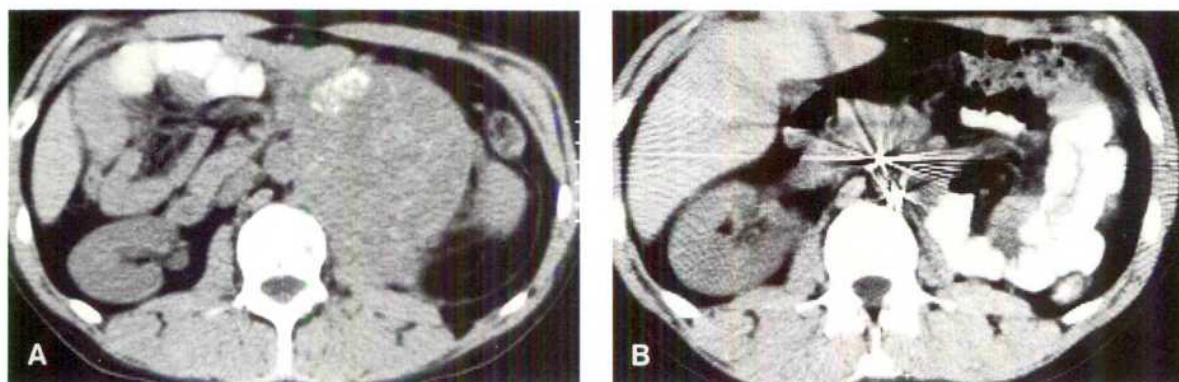


Fig. 1 (A) Pre-operative, post-chemotherapy CT scan of metastatic yolk sac tumour. (B) Follow-up CT scan 3 years later showing severe image degradation from stainless steel ligacclips.

PDS ligating clips were visible as linear radio opacities on early post-operative CT scans but were not associated with any radiological artefacts

(Fig. 2). Early post-operative scans unexpectedly revealed 1 patient to have a large lymphocele.

On later scans, PDS clips were still visible in 6

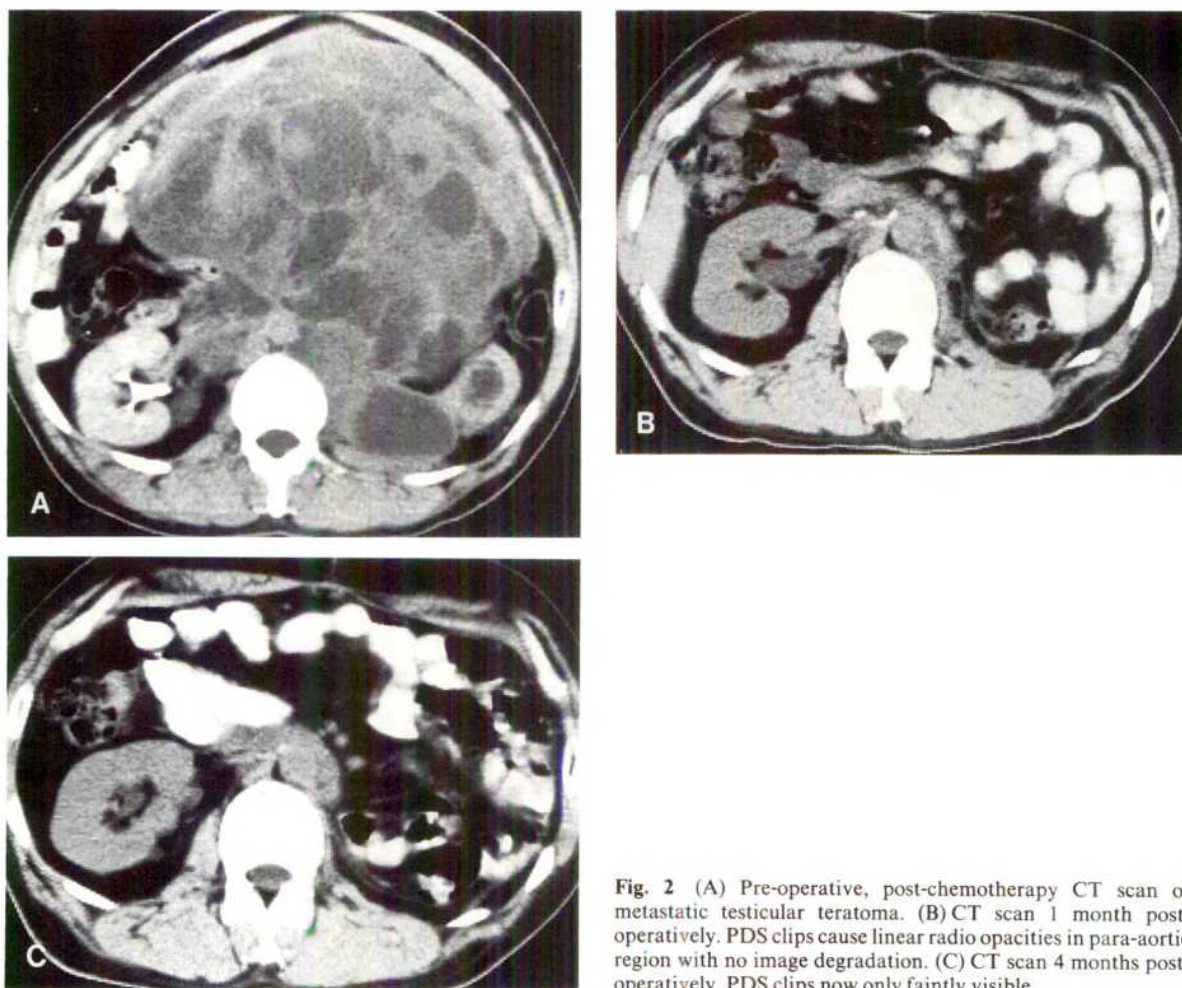


Fig. 2 (A) Pre-operative, post-chemotherapy CT scan of metastatic testicular teratoma. (B) CT scan 1 month post-operatively. PDS clips cause linear radio opacities in para-aortic region with no image degradation. (C) CT scan 4 months post-operatively. PDS clips now only faintly visible.

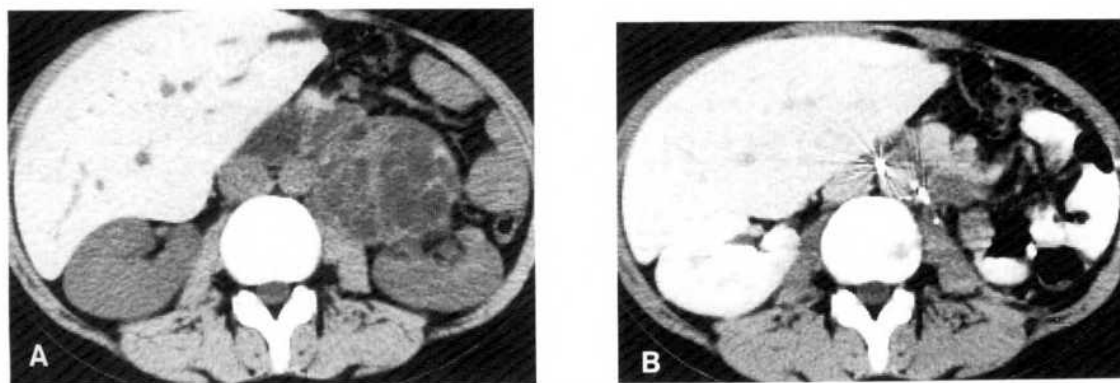


Fig. 3 (A) Pre-operative, post-chemotherapy CT scan of metastatic teratoma in a patient with thalassaemia (note bright liver from iron deposition). (B) Post-operative appearances of titanium ligacips showing image degradation.

patients but were fainter (Fig. 2) than on earlier scans, in keeping with progressive absorption. In 4 patients scanned at 6 months they had disappeared.

Titanium ligating clips were associated with CT artefacts (Fig. 3). Although these artefacts were similar to those seen with conventional stainless steel clips, they were of lesser intensity.

Unlike metallic clips, PDS clips have a locking mechanism which necessitates circumferential dissection of any pedicle prior to application of the clip.

One patient who was noted to have a progressive hydronephrosis on post-operative CT was re-explored and found to have differentiated teratoma within the ureter.

Discussion

In 1908 Cushing used a small U-shaped piece of silver wire held in the jaws of a haemostat to control bleeding and a standardised silver clip and applicator were soon to follow (Cushing, 1911). Stainless steel ligating clips were subsequently developed and although they have been widely employed for several years, it is now well recognised that they degrade subsequent CT as well as magnetic resonance images (MRI). For many patients undergoing radical cancer surgery, follow-up is likely to include and may depend upon post-operative CT or MRI. It would therefore be preferable in such patients to avoid the use of stainless steel ligating clips because the image distortion on subsequent scanning will significantly impair the diagnostic value of the investigation.

★ In patients with metastatic NSGCT we have performed para-aortic lymphadenectomy for residual masses following platinum-based combination

chemotherapy (Hendry *et al.*, 1987). Although the risk of local recurrence is low following post-chemotherapy para-aortic lymphadenectomy, post-surgical CT scanning is important in this disease to exclude or confirm the presence and anatomical location of recurrent disease should it occur, and it is crucial in the follow-up and management of higher risk patients. The risk of recurrence in these patients is related to various prognostic factors (Hendry *et al.*, 1987), including the persistence of elevated markers following chemotherapy, the presence of undifferentiated teratoma in the resected specimen, and the inability to obtain a complete surgical clearance at operation. Although we have found that stainless steel ligating clips do facilitate para-aortic lymph node dissection, we have been disappointed by the artefacts produced by them on our patients' follow-up CT scans and this prompted the present study.

Polydioxanone is a synthetic absorbable polymer which can be converted into a flexible monofilament suture or moulded into ligating clips. *In vivo* it degrades by hydrolysis into soluble components with minimal local tissue reaction. Although widely employed as a suture, experience with the ligacips is still limited.

Polydioxanone ligacips were straightforward to use, although it was important to dissect the tissues sufficiently to enable the locking mechanism to engage. For this reason these ligacips were a little less easy to apply than either stainless steel or titanium clips, but when the locking mechanism was engaged the clips were secure. Although an automated applicator containing multiple PDS ligating clips is available, in this study PDS clips were loaded and used individually, reloading the applicator after each clip placement.

On early post-operative CT scans PDS ligating clips were visible as linear radio opacities. These were less intense than those seen with metallic ligating clips and were never associated with any CT artefacts as seen with stainless steel ligating clips. On the later post-operative CT scans PDS clips were either faintly visible or else had disappeared, in keeping with progressive absorption.

The CT imaging characteristics of PDS and metallic ligating clips have been studied in an experimental model (Weese *et al.*, 1984; Gross *et al.*, 1985). Maximal CT image degradation was found with tantalum and lesser degrees with stainless steel and titanium respectively. Only minimal artefact was seen with PDS.

We found the titanium ligating clips easy to apply and secure and in the present study we used an automated applicator containing multiple clips. These were visible on subsequent CT scans and were associated with image artefacts which resembled those seen with stainless steel clips but which were less intense.

The patient who was subsequently found to have intraureteric differentiated teratoma had had an *en bloc* resection of his post-chemotherapy residual mass with the infrarenal vena cava at his first laparotomy. In retrospect this intraureteric tumour was probably present at that time. No other patient in this group was identified as having recurrent disease during the study period.

This study focused on the effects of various ligating clips upon subsequent CT scanning. We have confirmed in patients that although PDS clips are visible on CT prior to absorption, they do not cause any artefacts; titanium ligating clips, al-

though possessing better imaging characteristics than stainless steel, are nonetheless associated with some artefact production. Although we have not examined the effects of these materials on subsequent MRI scans, metallic clips may move in the magnetic field and are also known to induce serious artefacts. An absorbable ligating clip would also be preferable in this instance. When ligating clips are employed per-operatively and post-operative CT scanning is important, PDS is the material of choice.

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PAEDIATRIC UROLOGY

Antenatally Detected Pelviureteric Junction Obstruction. Is Non-operation Safe?

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Summary—We report follow-up data (minimum of 1 year) on 63 kidneys with antenatally detected pelviureteric junction obstruction, as defined by renographic criteria. The condition was bilateral in 10 patients (*i.e.* 20 kidneys), 2 patients had unilateral obstruction with contralateral multicystic dysplastic kidneys, and 41 patients had unilateral obstruction with a normal contralateral kidney. In the latter group, 29 (71%) had good function ($>40\%$) at initial assessment.

Of the 63 kidneys, 24 (38%) were operated upon following initial assessment, mainly for impaired function. Of 39 patients, initially managed non-operatively, 8 (21%) were operated upon subsequently: 3 for deteriorating function (2 of whom have been reassessed and both have regained their lost function) and 5 for other renographic or ultrasonic indications).

Of the original 63 kidneys, 31 (49%) continue to be managed non-operatively; 16 of these (52%) show improving ultrasound appearances, 8 of 17 studied show improved drainage, and all unilateral cases have stable good function.

It is concluded that non-operative management of selected cases of antenatally detected pelviureteric junction obstruction is safe.

In 1985 the prevailing practice of operating routinely on infants with antenatally detected hydronephrosis was questioned (Ransley and Manzoni, 1985). They advocated a more conservative approach, based on the isotopic assessment of function, reserving surgery for those kidneys demonstrating a significant loss of function. In common with others (Arnold and Rickwood, 1990), we have followed their criteria in the management of antenatally detected pelviureteric junction (PUJ) obstruction.

The definition of obstruction in this context remains controversial. We have used renographic criteria (O'Reilly *et al.*, 1978) and have excluded patients with pelvicaliceal hydronephrosis but normal drainage on renography.

This study was undertaken to evaluate the outcome of non-operative management of antenatally detected PUJ obstruction in infants followed up for a minimum of 1 year.

Patients and Methods

The study was based on 53 infants presenting to the regional paediatric urological service in Leeds between January 1983 and March 1989. All patients with antenatally detected PUJ obstruction who had either undergone surgery or been followed up until 1 year of age were included.

Of the 53 infants, 41 had unilateral obstruction, 10 bilateral obstruction and 2 had unilateral PUJ obstruction associated with a contralateral multicystic dysplastic kidney; thus 63 kidneys with pelviureteric junction obstruction are reported (Fig.).

The infants were referred from district hospitals throughout the Yorkshire region and the timing of their initial postnatal imaging was not uniform. For those infants born in Leeds, an early micturating cystogram was performed routinely in the first part of the study. More recently, however, cystography has been confined to male infants with bilateral pathology, to infants with ureteric dilatation evident on ultrasound, or those whose ultrasound

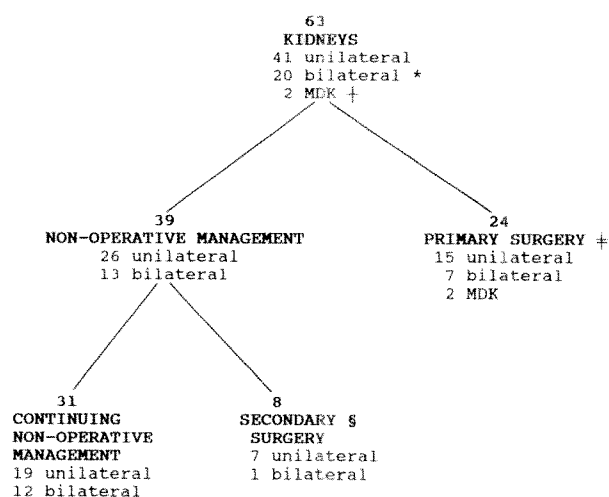


Fig. Management of 63 kidneys with antenatally detected pelviureteric junction obstruction.

*20 kidneys in 10 patients.

†MDK = Contralateral multicystic dysplastic kidney.

‡Surgery as initial form of management.

§Surgery followed a period of non-operative management during which progress was unsatisfactory.

appearances were not strongly suggestive of PUJ obstruction.

From 1 month of age, imaging followed a more consistent pattern. Diuresis renography was performed together with a repeat ultrasound scan at 1 month of age and these investigations are regarded as the initial investigations for the purposes of this study. Thereafter, ultrasound scans were repeated at intervals of 3–6 months, with renography at 1 year of age and annually thereafter as indicated.

Obstruction was defined by renography in 54 cases and by antegrade pyelography in 4 infants with massive hydronephroses. In 2 kidneys obstruction was inferred from the combination of impaired function on DMSA scan and ultrasound appearances of gross dilatation. In 1 instance obstruction was suggested by intravenous urography and in another 2 by initial ultrasound appearances, but confirmed by renography after a period of non-operative management.

The renographic diagnosis of obstruction was defined as a flat or rising curve on the renogram 20 min after injection of isotope (equivalent to type 11, 111a or 111b) (O'Reilly *et al.*, 1978); infants with normal drainage on renography (O'Reilly type 1 curve) were not included in the study. The degree of obstruction was subdivided according to the response to frusemide injection 20 min after the isotope. DTPA (^{99}Tc -diethylene-triaminepenta-

acetate) was used throughout the duration of the study. In addition, ^{131}I Hippuran was used in the earlier years and MAG3 (^{99}Tc -mercapto-acetyl-triglycine) has been in use since 1988.

Figures for differential function were derived either from the uptake curves of the dynamic studies or, in some instances, from static DMSA (^{99}Tc -dimercaptosuccinic acid) images.

Patients were divided into 3 groups on the basis of differential function: preserved function ($>40\%$), impaired function ($15\text{--}40\%$) and poor or non-function ($<15\%$).

Figures for differential function for unilateral and bilateral obstruction are reported separately because assessment of relative renal function is valid only in the former group, where the contralateral kidney can serve as a control. The unilateral group included 3 patients with contralateral vesicoureteric reflux (Table 1), but in the remainder the contralateral kidney was entirely normal. In addition, there were 2 patients with contralateral multicystic dysplastic kidneys. Associated urological and non-urological anomalies are listed in Table 1.

The follow-up data are those most recently available. In kidneys managed non-operatively, follow-up ranged from 12–36 months (median 18). In those operated upon, follow-up ranged from 3–72 months of age (median 29).

Results

Initial assessment

Of the 41 patients with unilateral obstruction, function of the obstructed kidney was preserved ($>40\%$ differential function) in 29 kidneys (71%);

Table 1 Associated Anomalies

Urological	
contralateral VUR (2 Grade I, 1 Grade III)*	3
contralateral multicystic dysplastic kidneys	2
ipsilateral VUR (Grade III)	1
ipsilateral vesicoureteric junction obstruction	1
partially patent urachus	1
prominent utriculus masculinus	1
Non-urological	
Beckwith-Wiedemann syndrome +	1
imperforate anus + talipes	1
bilateral undescended testes	1
bilateral communicating hydroceles	1

*VUR = vesicoureteric reflux (International Reflux Study Committee (1981) grading).

+ Exomphalos with macrosomia.

it was impaired (15–40% function) in 10 kidneys (24%) and poor (<15% differential function) in 2 kidneys (5%). Of the patients with bilateral obstruction, function was preserved (>40%) in 16 (80% of kidneys); it was between 15 and 40% in 3 patients (15% of kidneys) and poor (<15% differential function) in 1 (5% of kidneys) (Table 2). In the 2 patients with unilateral PUJ obstruction and contralateral multicystic dysplastic kidney, renal function was confined to the obstructed kidney.

Renographic drainage in response to diuresis showed no response (type II) (O'Reilly *et al.*, 1978) in 18 kidneys (29%), partial response (type IIIb) in 23 kidneys (37%) and no drainage prior to injection of diuretic, but with a good response to diuresis (type IIIa) in 13 (21%); there were no data for 9 kidneys (14%). All 13 patients with a type IIIa curve had good function and ultrasound appearances showed only mild or moderate dilatation.

Initial ultrasound appearances showed severe hydronephrosis in 27 kidneys (43%), moderate hydronephrosis in 19 (30%) and mild in 15 (24%), with data missing on 2 kidneys.

Micturating cystograms were performed on 36 infants. Six abnormalities were shown (Table 1), of which only the 3 patients (8%) with vesicoureteric reflux (1 bilateral, 2 unilateral in the contralateral ureter) are considered significant.

Initial management (Fig.)

Surgery. Of the 41 patients with unilateral PUJ obstruction, 15 were managed surgically in the first instance. Two underwent nephrectomy because the affected kidney contributed less than 10% to total renal function; in 1 of these a percutaneous nephrostomy was inserted as part of the initial assessment. The remaining 13 underwent an Anderson-Hynes dismembered pyeloplasty. The principal indication for surgery was impaired function (<40%) in 9 patients. Of the 4 patients who underwent pyeloplasty despite preservation of function, 2 had clinically apparent hydronephrosis, so a percutaneous nephrostomy was inserted prior

to functional assessment, and 2 were managed before we were confident in the application of the criteria of Ransley and Manzoni (1985). The 2 patients with contralateral multicystic dysplastic kidneys underwent simultaneous nephrectomy and pyeloplasty.

Ten patients had bilateral obstructed kidneys (*i.e.* 20 kidneys). Pyeloplasty was performed on 7 kidneys: 4 kidneys in 2 boys with bilateral gross hydronephrosis (3 following percutaneous nephrostomy), 2 for reduced function, and 1 for gross hydronephrosis with only partial drainage on renography. The age at operation ranged from 1–6 months (mean 2.9).

Non-operative management. Of the 41 infants with unilateral obstruction, 26 were initially managed non-operatively. In the group with bilateral obstruction, 13 kidneys in 8 patients were initially managed non-operatively.

Outcome of non-operative management

Of the 26 patients with unilateral obstruction which was initially managed non-operatively, 7 (27%) have subsequently required surgery. The indications for this "secondary surgery" varied. Three exhibited reduction of differential function on follow-up renography. The other 4 had stable function, but 1 exhibited a deteriorating drainage curve on renography, 1 had deteriorating ultrasound appearances, and the remaining 2 showed persisting severe hydronephrosis on ultrasound associated with only a partial response to diuresis on renography.

One patient with bilateral obstruction was operated upon after a period of non-operative management. Renography at 1 month of age showed only a partial response to diuresis. Left pyeloplasty was performed because the ultrasound appearances of severe hydronephrosis persisted at 6 months of age. The right kidney initially showed mild dilatation and has improved without surgery.

The overall results of non-operative management are summarised in Table 3. The outcome has been assessed at a minimum of 1 year of age, using ultrasound to assess dilatation and dynamic renography to assess differential function and drainage. Of a total of 63 kidneys in the study, 31 (49%) are being successfully managed non-operatively after a minimum of 1 year's follow-up. Of these 31, 16 (52%) show improving ultrasound appearances, 9 of 17 studied show improved drainage on renography, and all unilateral cases have stable good function.

Table 2 Initial Differential Renal Function

Function	>40%	15–39%	<15%	Total
Unilateral	29	10	2	41
Bilateral	16	3	1	20
Total	45	13	3	61*

*Excludes the 2 patients with contralateral multicystic dysplastic kidneys.

Three patients with bilateral obstruction have shown a deterioration in function but continue to be managed non-operatively (Table 3). In 2 cases the deterioration in relative renal function is attributed to improvement in function in the contralateral kidney which has been operated upon; both unoperated kidneys showed improved ultrasound appearances and both now give a good response to diuresis. In the third patient the function is 39%; ultrasound shows improvement but drainage has deteriorated from a good to partial response to diuresis.

Only 3 kidneys show persistent severe dilatation on ultrasound but all show either a partial or a good response to diuresis on renography. All other kidneys in which drainage has been assessed show at least a partial response to diuresis and 3 show normal drainage.

Outcome of primary surgery

In patients who underwent surgery, initial post-operative investigations often showed little change, but improvement became apparent 1 year post-operatively and none has shown progressive deterioration on repeated post-operative assessment thereafter.

The only patient in whom function has deteriorated post-operatively has bilateral vesicoureteric reflux (ipsilateral grade 5, contralateral grade 3) and has suffered a urinary tract infection; function in the affected kidney is now less than 15%. In 1 patient the kidney shows no drainage in response to diuresis post-operatively, function is unchanged at 33%, and ultrasound appearances still show gross dilatation; however, antegrade pyelography reveals good drainage. (Table 3).

Outcome of secondary surgery

Of the 8 children operated upon following a period of non-operative management, the indication was loss of function in 3. Two of these have had function reassessed post-operatively and in both it has returned to the levels seen on initial assessment. All other post-operative studies in the patients who underwent secondary surgery show either no change or an improvement compared with their initial assessment at 1 month of age (Table 3).

Urinary tract infections

Antibiotic prophylaxis was given to 37 of the 53 patients and 5 of them (14%) developed urinary tract infections; 3 of the 16 patients (19%) who did

Table 3 Results

	<i>Function on Renography</i>			
	Continuing Non-operative (31)	Primary* Surgery (24)	Secondary† Surgery (8)	Total (63)
Improved	6	4	1	11
No change	10	9	3	22
Deteriorated	3‡	1	0	4
No data	12	10	4	26
	<i>Drainage on Renography</i>			
	Continuing Non-operative (31)	Primary* Surgery (24)	Secondary† Surgery (8)	Total (63)
Improved	9	13	1	23
No change	8	1	2	11
Deteriorated	1	0	0	1
No data	13	10	5	28
	<i>Ultrasound Appearances</i>			
	Continuing Non-operative (31)	Primary* Surgery (24)	Secondary† Surgery (8)	Total (63)
Improved	16	17	7	40
No change	15	2	0	17
Deteriorated	0	0	0	0
No data	0	5	1	6

*Surgery as initial form of management.

†Surgery followed a period of non-operative management during which progress was unsatisfactory.

‡All 3 had bilateral obstruction—see text.

not receive prophylaxis developed infections; this difference was not statistically significant (χ^2 test: $P > 0.1$).

Discussion

This study has demonstrated that the majority of kidneys with antenatally detected pelviureteric junction obstruction have good function at birth. Furthermore, we have confirmed others' experience (Bernstein *et al.*, 1988; Dejter *et al.*, 1988; Arnold and Rickwood, 1990; Ransley *et al.*, 1990) in that, by applying Ransley's criteria for selection (Ransley and Manzoni, 1985), antenatally detected pelviureteric junction obstruction can be managed non-operatively without jeopardising renal function. This contrasts with previously expressed concern that failure to operate may result in loss of function or, at least, failure of the kidney to develop to its full potential (Mayor *et al.*, 1975; McCrory *et al.*, 1980; Flake *et al.*, 1986; Dowling *et al.*, 1988). In fact, we found that delayed surgery was followed by recovery of function lost during a period of non-operative management in 2 cases.

During the period of this retrospective study, our protocol for investigating patients was modified. While relying primarily on renographic data, ultrasound has been a decisive factor in planning management in several cases, particularly those with bilateral obstruction.

There are several limitations in the techniques available for assessing the infant's urinary tract. We chose not to use a urodynamic method to define obstruction (Whitaker, 1973) because we felt it to be too invasive a procedure for the investigation of what is usually an incidental finding of uncertain significance in an asymptomatic patient; moreover, appropriate control data were not available.

We have, therefore, depended on diuresis renography to assess both drainage and function. We have defined obstruction using the original criteria of O'Reilly *et al.* (1978) because this allowed us to exclude kidneys with a type 1 curve, in which there is clearly no obstruction. We acknowledge that this may not agree with other definitions of obstruction (using, for example, renography with the diuretic injection preceding the isotope, renographically measured parenchymal transit times or urodynamic methods). Furthermore, as our data show, our definition of obstruction does not predict deteriorating function. However, it is well established and it was used consistently throughout the 7 years of the study.

Renography has several limitations in this group

of patients. Renal function matures significantly during the first few months of life and this may be a factor leading to changes in the drainage curves of kidneys studied renographically during this period (Homsy *et al.*, 1986). Other inaccuracies can arise as a result of difficulties in defining the area of interest, movement of the patient and variations in the state of hydration (Kass *et al.*, 1985; Homsy *et al.*, 1986); we did not control the degree of hydration in our patients undergoing renography. Furthermore, the assessment of drainage is recognised as unreliable in the presence of impaired function (O'Reilly *et al.*, 1984). Assessment of differential function is further limited in that it cannot be relied upon in cases where disease is bilateral.

In this study, 6 initially obstructed kidneys, each of which had a normal contralateral kidney, had differential function between 53 and 60% on follow-up; 4 continue on non-operative management and 2 have undergone surgery. The indication for operation in both cases was absence of drainage following diuresis at renography, associated with gross hydronephrosis on ultrasound; in both cases, however, renal function was preserved. The explanation for this apparent increase in function associated with obstruction is unclear. It is possible that obstruction *in utero* may, in some instances, stimulate a genuine increase in function in the affected kidney. A more probable explanation is that it is an artefact related either to the size of the kidney or to the handling of isotope by previously obstructed kidneys in this age group.

We believe that, despite its limitations, renography is the most appropriate method of identifying obstruction in these patients, but it is an invasive investigation and so there should be clear indications for its use. Antenatally detected hydronephrosis is usually an incidental finding. We did not feel it justified to repeat renography in patients who showed steady improvement on ultrasound assessment. Therefore, does the non-operative management of these patients have to rely solely on renography?

From our experience, certain simple observations can be made regarding investigations. Firstly, a good response to diuresis is likely to be associated with good function, less severe ultrasound appearances and a good outcome without surgery; indeed, many might not regard these as having been obstructed (O'Reilly *et al.*, 1978). Secondly, all patients treated by surgery, either initially or following a period of observation, had moderate to severe dilatation on ultrasound; this is consistent with observations that a renal pelvis which meas-

ures more than 1.2 cm (Ransley *et al.*, 1990) or 1.5 cm (Grignon *et al.*, 1986) in the anteroposterior (AP) plane is likely to require surgery. Thirdly, in the absence of ureteric dilatation, we did not find that a micturating cystogram yielded useful information, nor did it carry any morbidity. Fourthly, the incidence of urinary tract infection was relatively low in this study and antibiotic prophylaxis did not appear to be beneficial.

We intend to continue to use the criteria of Ransley and Manzoni (1985) in the selection of patients for surgery and non-operative management of antenatally detected PUJ obstruction. However, we believe that we can modify our management as follows:

- (1) If ultrasound appearances are strongly suggestive of PUJ obstruction, micturating cystography (with antibiotic prophylaxis) can be limited either to infants in whom the ureter is seen on ultrasound or to boys in whom there is bilateral upper tract dilatation. This should ensure the recognition of both of the more severe forms of vesicoureteric reflux and of boys with posterior urethral valves.
- (2) We believe that surgery is justified in cases of bilateral obstruction with equal function if there is marked hydronephrosis (> 1.2 cm AP diameter) on ultrasound and no response to diuresis.
- (3) Annual ultrasound examinations are probably adequate follow-up for kidneys which have good function and a normal or good response to diuresis on renography.
- (4) For kidneys which have normal function (> 40%) and partial or no response to diuresis, 6-monthly ultrasound examinations are advisable, with renography once or twice yearly if there is no improvement.

Evidence is slowly accumulating on the natural history of antenatally detected PUJ obstruction. Thus far it appears that appropriately selected patients can safely be managed non-operatively. Only by continued close surveillance throughout childhood, adolescence and into adult life will we learn whether this policy is safe in the long term.

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Blood and Urine Analysis in Patients with Intestinal Bladders

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Summary—A group of 183 patients whose urine was stored in pouches formed either wholly or partly from bowel was reviewed to establish abnormal biochemical and haematological factors and to assess the risk of infection. Minimum follow-up was 1 year (range 1–28.5, mean 3 years 8 months) and the mean age of the patients at follow-up was 16.5 years (range 4–43). Pouches were augmentation and substitution cystoplasties and complete reconstructions with bowel. Bowel segments were ileum (55 patients), colon (100) and mixed (28). Anaemia was found in 15 patients, folate deficiency in 2 and folate excess in 2. Definite hyperchloraemic acidosis was found in 25 patients and borderline results in 40. Most of these patients had colon in the pouch but 5 definite and 13 borderline cases had ileum only. Troublesome urinary infections occurred in 27.9% of patients; 3 developed renal stones and 22 developed pouch/bladder stones. Stones were usually associated with infection and/or staples. Delayed linear growth occurred in 20% of children in spite of a normal increase in weight; there was no difference in any of the measurements between those who grew and those who did not.

Segments of intestine have been used in lower urinary tract reconstruction for many years but only in the last decade have large numbers of patients received treatment. Many different types of reconstructive surgery are now available, ranging from modest augmentation cystoplasty to complete reconstruction by continent diversion. The common element is the use of a segment of intestine to form either all or part of the reservoir. There has been some anxiety amongst surgeons about the metabolic complications that might ensue. Would such reconstructions behave as conduits with relatively minor consequences, as ureterosigmoidostomies with major metabolic problems, or in a totally different and unpredictable way?

Patients and Methods

A protocol was designed, based on procedures that had been used informally for the follow-up of

patients with enterocystoplasties (Table 1). It might be considered excessive, but was designed to cover a wide range of complications.

All paediatric and adolescent patients whose urine was stored in reservoirs formed from bowel have been documented. Over the last 2 years the protocol has been reviewed prospectively and data have been retrieved on the haematological and biochemical profiles and the incidence of urinary infection.

All types of bowel and all patients were considered and they were then divided into 3 groups (Table 2). A total of 183 patients were followed up for at least 1 year. The maximum follow-up was 28.5 years (mean 3 years 8 months). Three patients had had renal transplants and 7 had reduced renal function that did not require dialysis.

Results

Haematology

There were 15 cases of anaemia (8.2%), 6 with an iron deficiency and the remainder showing non-

Table 1 Follow-up Protocol*Compulsory post-operative follow-up**3 months*

Full blood count, folate and B₁₂
 Urea and electrolytes, creatinine, chloride, bicarbonate and alkaline phosphatase
 Urine culture
 IVU (if kidneys were abnormal pre-operatively)
 Ultrasound (if kidneys were normal pre-operatively)

6 months

Full blood count, folate and B₁₂
 Urea and electrolytes, creatinine, chloride, bicarbonate and alkaline phosphatase
 Urine culture

1 year

Full blood count, folate and B₁₂
 Urea and electrolytes, creatinine, chloride, bicarbonate and alkaline phosphatase
 Glomerular filtration rate
 Urine culture
 Cystometrogram/pouch pressures
 Cystogram/pouchogram

Then 6-monthly

Full blood count, folate and B₁₂
 Urea and electrolytes, creatinine, chloride, bicarbonate and alkaline phosphatase
 Urine culture

Annual

Glomerular filtration rate
 Ultrasound
 Cystometrogram/pouch pressure studies
 Endoscopy (from 5 years)

Biennial

Cystogram/pouchogram
 Hand X-rays

IVU in a stable state before transfer to the adolescent clinic regardless of follow-up time.

Table 2 Patients' Ages and Bowel Segments Used in 183 Cases of Lower Urinary Tract Reconstruction

Age (years)	Intestinal segment	No.
4-11	Ileum	15
	Mixed	1
	Colon	34
12-17	Ileum	13
	Mixed	6
	Colon	37*
18+	Ileum	27
	Mixed	21
	Colon	29**

*indicates patient(s) with renal transplant.

specific indices (Table 3). There were no cases of macrocytic anaemia even in patients with Kock pouches, which are formed from 70 cm of ileum.

Biochemistry

The only significant abnormalities were found in the plasma chloride and bicarbonate levels (Table 4). Definite hyperchloraemic acidosis (HCA) was defined as plasma bicarbonate <18 mmol/l and chloride >108 mmol/l on at least 2 occasions. A borderline result was defined as an occasional abnormality in both indices or a consistent abnormality in 1. Definite HCA was seen in 13.7% of patients and borderline results in 21.9%. Although HCA was most common in those with large bowel in the reservoir (definite 15.6%, borderline 21.1%), the incidence in patients with ileum alone was only slightly less (definite 9%, borderline 23.6%). There was no association between chronic infection and HCA.

Changes in glomerular filtration rate (GFR) were seen only in cases of obstruction or in patients whose initial function was poor and for whom dialysis had been predicted. In patients with obstruction pre-operatively, the GFR improved after reconstruction. Deterioration in a previously normal GFR after reconstruction was invariably due to obstruction.

Urine bacteriology

Infection was the most serious symptomatic complication. Troublesome infections were frequent, symptomatic and proven, sometimes requiring continuous antibiotic prophylaxis. Symptoms included local pain, frequency, smelly urine, back-ache, and general symptoms of malaise and fever. Smelly urine alone was not a good guide as the mucus that is invariably present always confers an unpleasant smell.

It will be seen from Table 5 that infections were a common problem. Most patients were on intermittent clean self-catheterisation (ICSC) but the 26 patients who voided spontaneously and to completion incurred the same infection rate. Low dose prophylactic antibiotics were used in 21 patients. The organisms most frequently found were *Escherichia coli*, *Klebsiella aerogenes*, *Proteus* species and *Citrobacter freundii*.

Stones

The most significant complication of infection was stone formation (Table 5) and only 1 patient formed stones in the absence of infection. Pouch stones

Table 3 Haematology Results

Age (years)	Intestinal segment	No.	Haemoglobin		Plasma folate		Plasma B ₁₂	
			Low	High	Low	High	Low	High
4-11	Ileum	15	1					
	Mixed	1						
	Colon	34	5			1		
12-17	Ileum	13	1					1?
	Mixed	6						
	Colon	37	2*					
18+	Ileum	27	3		2+1?	2+1?		
	Mixed	21	2					1
	Colon	29	1					1

? = borderline case.

* indicates patient with renal transplant.

Table 4 Incidence of Hyperchloraemic Acidosis

Age (years)	Ileum			Mixed			Colon		
	Total no.	Definite	Borderline	Total no.	Definite	Borderline	Total no.	Definite	Borderline
4-11	15	2	5	1	0	0	34	4	12
12-17	13	0	3	6	0	2	37	8*	3
18+	27	3	5	21	0	6	29	8*	4*

* indicates patient with reduced GFR.

Definite hyperchloraemic acidosis is defined as plasma bicarbonate < 18 mmol/l and chloride > 108 mmol/l on at least 2 occasions. In borderline cases 1 electrolyte was abnormal, or both on 1 occasion only.

Table 5 Incidence of Urinary Infection and Stones

All patients	Infections		Stones	
	Troublesome (%)	Occasional (%)	Kidney (%)	Bladder (%)
Ileum	31	15	4	11
Mixed	36	15		18
Colon	24	30	1	11
Spontaneous voiders				
All types	30	8	0	0

occurred equally in both ileal and colonic pouches; mixed pouches had a slightly higher incidence. Eleven of 55 ileal pouch patients had Kock pouches which, by definition, contain metal staples: these

patients had 3 stones. It is difficult to explain why mixed pouches should have had more stones than the other 2 types (18 vs 11%).

We formed the clinical impression that stones

were sometimes associated with mucus retention in the pouch. Some of the stones were soft and little more than aggregates of mucus, whilst others were more solid. Renal stones were more common in patients with ileal pouches, again for unknown reasons.

Growth

Height and weight were measured in 60 children for at least 2 years pre-operatively and on at least 2 occasions post-operatively; 12 of these patients (20%) had delayed linear growth but maintained an increase in weight. The loss in height was a mean of 20.2 percentile points (range 11–40). There was no difference in any of the measurements, including glomerular filtration rate, between children who grew normally and those whose growth was retarded.

Discussion

The consequences of diverting urine through bowel have been widely studied and can be divided into 3 categories (renal, histological and metabolic). We found no renal damage directly attributable to urinary diversion. Removal of large segments of bowel, especially terminal ileum, from the gastrointestinal tract could result in macrocytic anaemia due to B_{12} and folate deficiency. Our relatively short follow-up revealed 2 (or possibly 3) cases of folate deficiency but there were 2 cases of raised plasma folate. No patient developed macrocytic anaemia.

In an experimental study of patients with reservoirs between 4 months and 8 years old, no disturbance in B_{12} or carotene metabolism was found (Canning *et al.*, 1989). However, in a study of Kock pouch patients followed up for periods ranging from 5 to 11 years, 6 of 17 patients were found to have borderline or subnormal plasma B_{12} levels that required supplements (Akerlund *et al.*, 1989).

Since the body stores of folate and B_{12} are high, and some absorption may continue because of bowel adaptation, clinical problems may be slow to develop. These factors should be monitored in all patients who have lost large sections of ileum and it would be better to identify the problem early rather than wait until macrocytic anaemia has developed. It has been shown experimentally that segments of bowel used as short conduits can absorb ions and drugs from urine, but clinical experience

has revealed few problems. Work in this unit has shown that ileal conduits lose absorptive capacity, probably as a result of profound villous atrophy (Sridhar *et al.*, 1983; Deane *et al.*, 1984). Similarly, colonic conduits present few metabolic problems, with histological change largely limited to inflammation (Moorcraft *et al.*, 1983).

The traditional method of storing urine in bowel has been the ureterosigmoidostomy and the metabolic consequences, particularly HCA, are well known. Some points might be relevant to more modern forms of reservoir. The speed of development and the severity of HCA are proportional to the surface area of colon and the duration of exposure (Hayward *et al.*, 1961). The full-blown syndrome of HCA with encephalopathy occurs only when there is concomitant hyperammonaemia. The bowel effluent may contain a high concentration of ammonia produced by faecal bacterial action on urine. However, absorbed ammonia is so rapidly metabolised by the liver that hyperammonaemia occurs only in liver failure or when the portal venous level is so high that the capacity of the liver is exceeded (Imler *et al.*, 1979).

The exact mechanism by which the metabolic changes occur is not fully known and absorption of ammonia and secretion of bicarbonate with exchange for chloride have been suggested in the case of ureterosigmoidostomies. If ammonia has a primary role (Koch and McDougal, 1988), it cannot be due to absorption alone because of the metabolism in the liver. Furthermore, ammonia itself is alkaline. However, absorption after conversion to ammonium chloride, or facilitation of chloride absorption by the presence of ammonia, would be theoretically possible. If production of ammonia in the bowel is important, the absence of faecal flora in a reservoir should make HCA uncommon. The maintenance of sterile urine would be of particular importance. In our patients there was no relationship between persistent infection and HCA.

An alternative suggestion, which is tenable for pouches, is that HCA is due to the secretion of bicarbonate in response to the arrival of an acid fluid in the colon with chloride reabsorption as an obligatory secondary factor (McConnell *et al.*, 1979). This mechanism could operate in all bowel reservoirs. In the present series, with only a short follow-up, the incidence of HCA was high. There was little difference in incidence between pouches containing colon and those formed of ileum alone. These findings are in broad agreement with those of Nurse and Mundy (1989a), who found that one-third of patients had hyperchloraemia and most

patients had metabolic acidosis with respiratory compensation on blood gas analysis. Conversely, our data do not support the findings of Akerlund *et al.* (1989), who found no alteration in arterial base excess or pH in blood gas analysis of 17 patients with a Kock pouch. The incidence is similar to the 50% noted in our long-term follow-up of patients with ureterosigmoidostomies (Silverman *et al.*, 1986). Since there are no faeces in the pouches, it seems unlikely that ammonia formation plays an essential part.

The incidence of urinary infection in our patients was high (24–36%). Although most patients were on ICSC, even those who voided normally were not exempt. This is higher than the 11% incidence of persistent bacteruria reported in the long-term follow-up of patients who were self-catheterising bladders without bowel augmentation (Diokno *et al.*, 1983). The consequences, apart from morbidity, are unknown. Kass *et al.* (1981) reported that infection with ICSC was harmless except in the presence of high grade reflux, when 60% of patients suffered renal damage. In conduits, persistent infection has been associated with progressive renal scarring (Bergman *et al.*, 1979). The present series has shown the risk of stone formation. In addition, there is the ever present fear that pouches may be prone to neoplasia, in the same way that ureterosigmoidostomies are; bacteria may play a role in the production of carcinogens in urine (Silverman *et al.*, 1986; Stewart, 1986). In reservoirs, more severe histological changes and higher levels of urinary nitrosamines have been correlated with heavy mixed growth on culture (Nurse and Mundy, 1989b).

The fact that, to date, there has been no major incidence of renal damage or neoplasia in pouches should not give rise to complacency. It was many years before these complications were recognised in conduits and ureterosigmoidostomies.

We are only just becoming aware of the unpredictable complications associated with our reconstructions. A chance finding was the 20% incidence of delayed linear growth in children with a normal increase in weight. This was not predicted and appropriate measurements were not being made routinely. There was no association with acidosis, intercurrent illness or operative complications and we have not identified either a cause or a group of children especially at risk. This important finding underlines the need for constant vigilance in patients with bowel reconstructions.

The problem may lie in bone development, even though we did not find abnormalities in alkaline

phosphatase. Osteomalacia is known to be associated with chronic HCA (Harrison, 1958). In rats, Koch and McDougal (1988) found that the femurs of animals with ureterosigmoidostomies were shorter at sacrifice than the femurs of controls, but the differences were not significant. The ages of the rats were not given, although it is known that they were still growing.

The high incidence of complications, although most were fairly minor, justifies the detailed follow-up protocol that we have used. We now measure height and weight at every visit until the patients are 20 years old, and an annual plain abdominal X-ray is carried out. Plasma B₁₂ and folate are not measured until the fourth year of follow-up.

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Application of the Onlay Island Flap Urethroplasty to Penile Hypospadias with Severe Chordee

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Summary—The onlay island flap urethroplasty was originally used to repair anterior hypospadias without chordee and was later used to repair penile hypospadias with a well developed urethral plate exhibiting little or no chordee after release of skin tethering. It is possible to treat all cases of penile hypospadias even with severe chordee by releasing the chordee without dividing the urethral plate and by reconstructing the urethra with an onlay island flap.

The technique of Ransley *et al.* (1990) for repairing epispadias demonstrates the possibility of releasing severe chordee without dividing the urethral plate. The plate is left attached distally to the glans and proximally to the epispadiac meatus but is dissected free from the corpora. Reduced to the mucosa alone, the urethral plate lengthens, narrows considerably, and no longer causes chordee. Despite extensive dissection, the blood supply to the plate remains adequate. The flip-flap technique of Devine and Horton (1977) and the technique of Koyanagi *et al.* (1983) for repairing hypospadias also show that it is not necessary to divide the urethral plate in order to release the chordee. We therefore decided to treat proximal hypospadias with chordee by releasing the chordee without dividing the urethral plate and by reconstructing the urethra with an onlay island flap.

Operative Procedure

A traction suture is placed in the glans. Epinephrine (1/100 000) and lignocaine (1%) are injected along the line of the incision, which begins just behind and around the ectopic meatus and is extended on each side of the urethral plate. It must be remembered that after dissection, the urethral strip will lengthen and become narrower but between the 2

parallel incisions it must be sufficiently wide (8 mm approximately for a 2-year-old boy). Distally the incisions are extended on to the glans towards the site of the new urethral meatus. Laterally a subcoronal (5–6 mm) incision is extended to the corner of the foreskin. It is completed by a chevron incision to leave bilateral mucosal darts which will be transferred in a ventral direction as described by Firlit (1987). The shaft skin is taken down.

Sometimes dissecting the skin releases superficial tethering and straightens the penis sufficiently. Dissection behind the plate can then be avoided. The urethra is reconstructed with an onlay island flap.

If the saline erection test demonstrates a persistent curvature, the urethral plate must be lifted up from the corpora. The chordee is associated with vestigial dysgenetic fibrous tissue resulting from aplasia of the corpus spongiosum. This fibrous tissue surrounds the urethral meatus and extends in a fan shape to the undersurface of the glans. If the fibrous area is well delineated laterally by 2 large vascular and fibrous pillars, its medial part, under the mucosa of the urethral plate, is often very thin. It is, however, adherent to the plate and to the corpora and this is an essential factor in the development of chordee.

Buck's fascia is incised laterally in a healthy area to visualise the blue, shiny, bulging tunica albuginea. Keeping contact with this, fine scissors are slipped behind the plate which is lifted up (Fig. 1).

All of the fibrous tissue must then be resected, not only the 2 lateral pillars but also the fibrous tissue on the undersurface of the urethral plate. The dissection must be extended proximally to the normal urethra surrounded by normal spongiosum. Distally, glans wings are developed and generously mobilised by sharply defining the path between the tips of the corpora and the glans cap (Fig. 1). A divot of glans tissue is removed from the undersurface of the glanular segment of the urethral plate as described by Devine and Horton (1977). This allows the plate to fit smoothly back on to the surface of the corpora. Finally the urethral plate, purely mucosal and approximately one-third longer and narrower (Fig. 2), is completely free between its 2 ends. After removal of all restricting fibrous tissue even under the plate, an erection test assesses straightening of the penis.

Chordee is usually eliminated completely. If some degree persists, a further procedure is needed to reduce corporal asymmetry (glans tilt, dorsal plication or even dermal or tunica vaginalis grafts). In our experience, dissection under the urethral plate is often necessary, but division of the plate is seldom indicated (Fig. 2).

Urethroplasty is then performed with an onlay island flap as described by Elder *et al.* (1987).

Skin coverage is not difficult with the dorsal longitudinal split to enhance a ventral midline closure. The glans wings, fully mobilised, are easily sutured over the glanular urethra, with subglanular

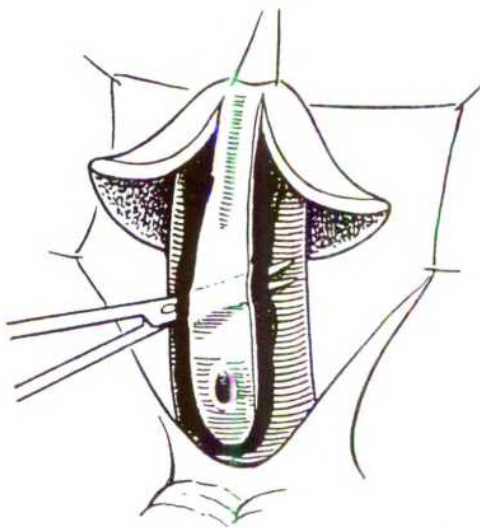


Fig. 1 After incision of Buck's fascia laterally in a healthy area, fine scissors are slipped behind the plate which is lifted up.

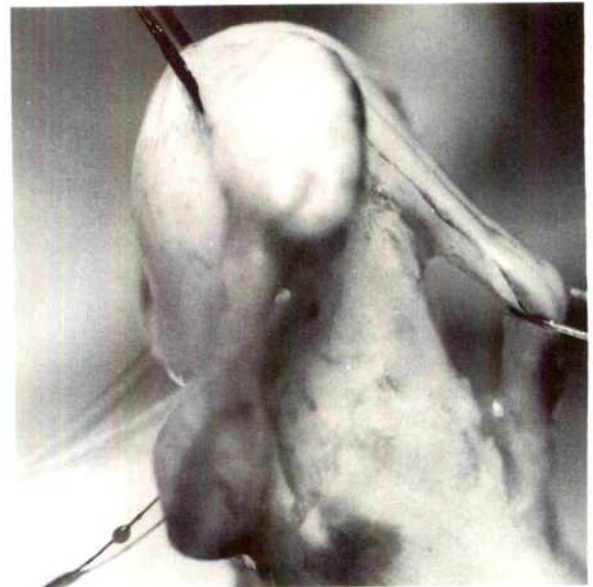


Fig. 2 Erection test demonstrates complete release of the chordee: the urethral plate is too long.

reconstruction of the mucosal collar. We use fine interrupted absorbable sutures (Maxon 6 and 7/0). An 8 F silicone catheter is inserted into the bladder through the repaired and normal urethra and this allows continual drainage of urine into nappies for 7 days, although the patient may leave hospital after 2 days.

Results

Between September 1989 and June 1990, 22 patients were managed by this procedure. They were between 12 and 26 months old and all had a proximal penile hypospadias with marked chordee. After releasing the chordee the meatus was between the middle of the penis and the base of the shaft in front of the scrotum. We have not used this operation for scrotal or perineal hypospadias, although it could be suitable in combination with the use of the smooth hairless epithelial tissue between the 2 parts of the scrotum to bring the meatus out to the penoscrotal junction.

One of our patients had a fistula which disappeared spontaneously and another had a small necrotic area in the skin covering the new urethra but it healed without fistula. There was no stenosis. All patients have a good functional and cosmetic result with a well reconstructed glans and apical meatus.

Discussion

The onlay island flap urethroplasty without dividing the urethral plate is easy, quick and gives excellent results. Initially it was used only for anterior hypospadias without chordee (Elder *et al.*, 1987) (50 cases: 1 fistula, 1 flap necrosis). Hollowell *et al.* (1990) then extended the technique to hypospadias with a well developed urethral plate exhibiting little or no chordee after release of skin tethering (31 cases: 8% complications).

In the case of penile hypospadias, our results show that even severe degrees of chordee with a urethral plate which is thin, adherent and poorly developed can be alleviated without dividing the plate, as in Ransley's technique for epispadias (Ransley *et al.*, 1990). These types of hypospadias may benefit from the onlay island flap urethroplasty described by Elder *et al.* (1987) with its technical advantages and low complication rate.

This technique is easier to perform than the tubularised transverse preputial flap and all risk of proximal stenosis is eliminated because there is no circular anastomosis.

With this procedure there is no risk of meatal stricture or prolapse (which is not the case with a bladder mucosal graft), probably because 2 flaps of the same histological structure are used.

Fistulas are less likely to develop and extensive dissection of the urethral plate facilitates the placing of lateral sutures. Covering the urethroplasty with the pedicle of the preputial flap as a first layer also provides protection from fistula formation.

As far as the long-term results of the flip-flap technique are concerned, there is probably little risk that the urethral plate reduced to the mucosa will fail to grow normally. We feel that the good results achieved initially in our patients will be maintained in the future.

Follow-up in this series has been too short for definitive conclusions to be drawn, but we think

the technique is promising. It represents a significant departure from our previous approach to the management of proximal hypospadias with chordee. We now try to release the chordee without dividing the urethral plate and only if this proves impossible do we divide it. This new technique can therefore replace the flip-flap technique or the tubularised urethroplasties with pedicle flap or free grafts at least in cases of penile hypospadias.

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Case Reports

Carcinoma of the Prostate Presenting as Impotence

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Case Report

A 61-year-old man was referred for investigation of erectile failure. His impotence had been of gradual onset and associated with wasting of his left thigh and weight loss. Examination revealed a palpable bladder, marked wasting of the left quadriceps (Fig. 1) and a T4 malignant prostate. Raised serum prostatic markers and isotope bone scanning confirmed multiple secondary deposits. Local tumour extension causing destruction of the sacrum was seen on CT scanning of the pelvis (Fig. 2). Transurethral resection of the prostate corrected the bladder outflow obstruction and confirmed the prostatic carcinoma. The patient subsequently elected to undergo orchiectomy and has shown an excellent response, with disease markers returning towards normal.

Comment

Pelvic malignancy is an uncommon cause of impotence. Local invasion and neural destruction by the primary tumour are the likely causes in this case. The marked wasting of the left quadriceps



Fig. 1 Muscle wasting of left thigh.

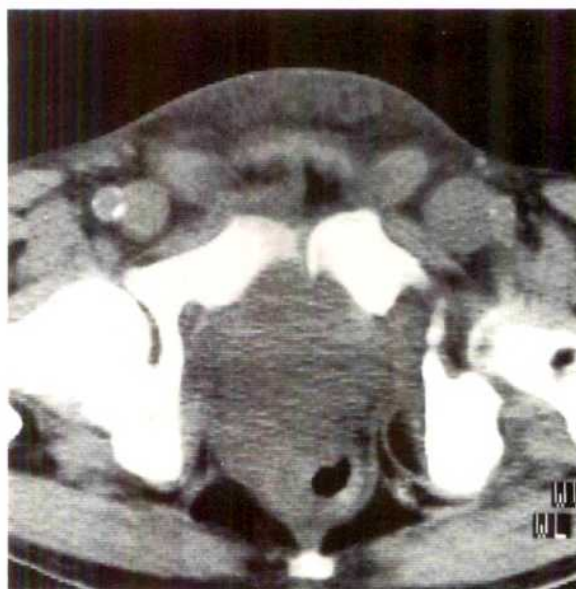


Fig. 2 CT scan of pelvis showing bony destruction of pelvis by prostatic carcinoma.

would seem to support this pathogenesis. It is also interesting to note that following orchiectomy there has been some return of the muscle bulk but we still await improvement in erectile function.

With the recent interest in treating patients with disseminated disease by total androgen blockade and the wish to preserve potency, this case serves as a reminder that erectile failure associated with prostatic cancer may not simply be a side effect of treatment but a sign of local disease progression.

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Verrucous Carcinoma of Vesical Diverticulum

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Case Report

A 74-year-old Chinese medicine salesman complained of dysuria and painful micturition for 1 week. Sonography revealed a septum in the sagittal plane which divided the bladder into 2 equal chambers communicating with each other through the central orifice of the septum. There were stones in each chamber. Intravenous urography showed obstruction of the distal ends of bilateral ureters

and a radio-opaque shadow located over the lateral margin of the bladder. Cystography revealed the 2 chambers of the bladder (Fig. 1). Litholapaxy was performed and a Chinese herbal drug (like ginseng) was found in the core of the stones. A large warty, exophytic mass was discovered after removing the stones in the left chamber and partial cystectomy with resection of the left chamber and left ureteroneocystostomy were performed (Fig. 2). Pathological examination revealed verrucous carcinoma.

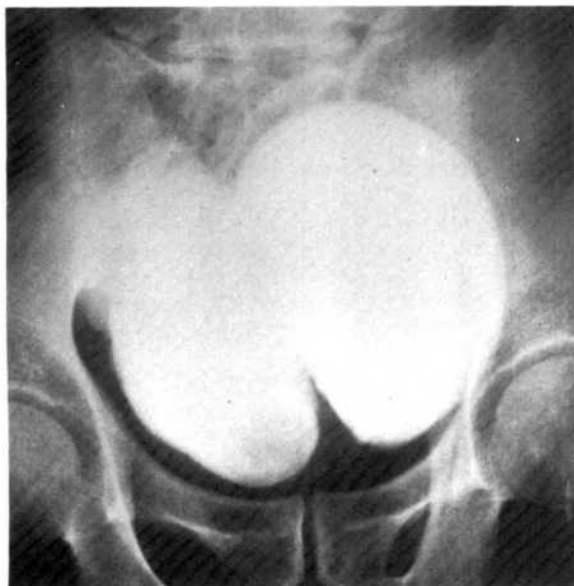


Fig. 1 Cystogram showing diverticulum (D).

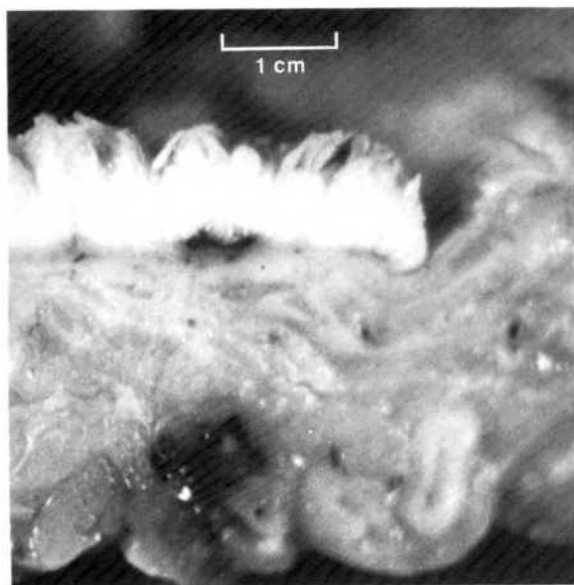


Fig. 2 Cross-section of the verrucous carcinoma shows no extension into the underlying bladder wall. No muscle layer is noted.

Comment

Verrucous carcinoma, a variant of well differentiated squamous cell carcinoma, is rarely found in the urinary bladder and is often associated with a history of schistosomiasis (El-Sebai *et al.*, 1974; El-Bolkainy *et al.*, 1981).

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Renogastric Fistula

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Case Report

Mrs L., aged 60 years, described a long history of left loin pain without urinary symptoms. Abdominal examination by ultrasonography demonstrated hydronephrosis of the left kidney. Intravenous urography showed a normal right kidney and a non-functioning left kidney. The urine was sterile. A left retrograde ureteropyelogram did not show the left kidney. Percutaneous injection of contrast into the mass revealed an abnormal kidney and the stomach (Fig.). Gastroscopy revealed ulceration on the greater curvature but the barium meal was normal. The mass was explored: the kidney was pyonephrotic and was removed; the stomach was sutured.

Histological examination confirmed a pyonephrotic kidney with a renogastric fistula without evidence of tumour or tuberculosis.

The patient made a rapid and full recovery.

Comment

Renogastric fistulas are extremely rare. In 1973 Bissada *et al.* found only 7 cases in the literature, although Dunn and Kirk (1973) added another case

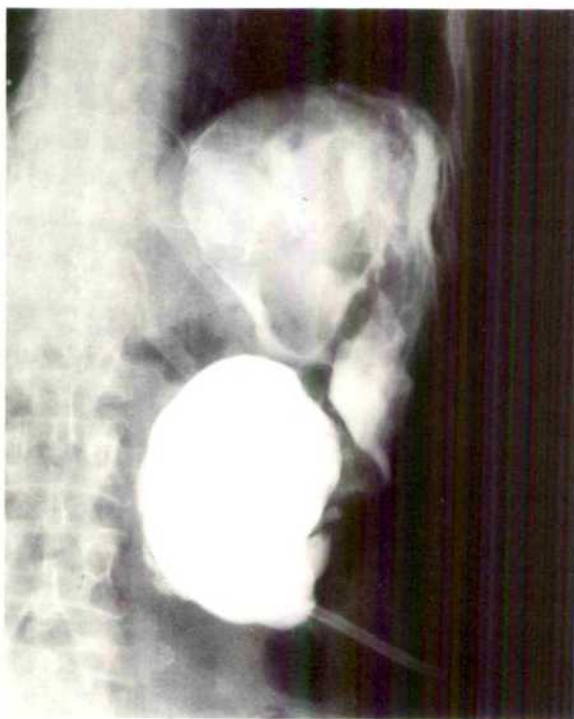


Fig. Renogastric fistula.

that same year. Three other cases have been reported (Milling and Santer, 1978; Sacerdoti *et al.*, 1982; Casselman and Maes, 1988). Pyonephrosis (with or without stones) is the usual cause of the fistula; other causes are tuberculosis, ruptured echinococcal cyst and perforated gastric ulcer.

Acknowledgement

We thank Mr B. Leger for his help.

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Diagnosis and Management of Large Seminal Vesicle Stones

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Seminal vesicle stones are rare and there are few reports in the literature. Only 1 patient with recurrent huge seminal vesicle stones has been seen in this hospital.

Case Report

H.Y.Y., a 53-year-old Chinese male, presented with testicular, perineal and groin pain of several years' duration; it was severe enough to interfere with working and sleeping. He was an engineer with a past history of rheumatic heart disease, mitral valve stenosis, atrial fibrillation, heart failure and cerebral arterial embolism. In 1970 and again in 1973, he had undergone seminal vesiculectomy to remove stones.

The recurrent stones were readily palpable on rectal examination. X-ray (Fig. 1) showed 2 further stones in the seminal vesicle area. Intravenous urography showed normal kidneys and ureters.

The stones were removed under epidural anaesthesia by a transrectal approach in November 1989. One stone measured $3.2 \times 2.8 \times 2.2$ cm and weighed 15 g. The other was flat, measuring $2.5 \times 2.0 \times 0.7$ cm and weighed 3.0 g (Fig. 2). A drain was left in the opened vesicle and brought out alongside the anus. The rectal incision was closed in 2 layers with 3/0 catgut. The procedure took 1 h, the blood loss was minimal and the patient made a rapid recovery. The wound drain was removed on day 7 and the patient was discharged.



Fig. 1

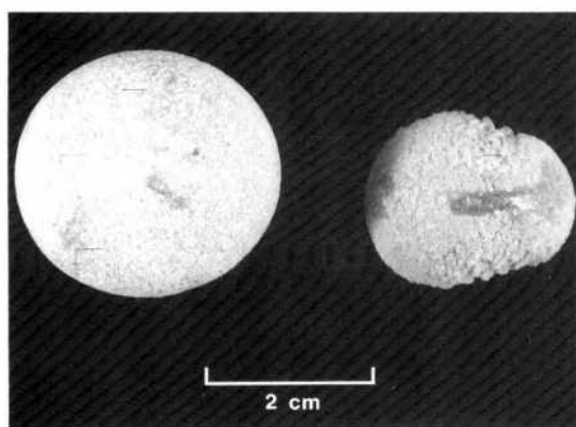


Fig. 2

In view of the recurrent nature of these stones a vesiculectomy would have been performed but this patient's significant medical problems made it unsafe to do so.

Comment

Seminal vesicle stones are rare. They usually occur in seminal cysts in men over 40 years of age and are often associated with seminal vesiculitis.

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nisolone). Her left kidney has returned to normal and CT scan of the bladder demonstrated disappearance of the submucosal tumour. After 3 years' follow-up she has no evidence of recurrence.

Comment

Only about 20 cases of primary malignant lymphoma of the bladder have been reported in Japan (Gohji *et al.*, 1985). A wide variety of treatments, ranging from radiotherapy to radical cystectomy, has been adopted with good results (Aigen and Phillips, 1986). Since malignant lymphoma is a systemic disease, however, surgical intervention is indicated only to treat uncontrollable irritative symptoms of the bladder. Radiotherapy or systemic chemotherapy should be used.

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Primary Malignant Lymphoma of the Bladder

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Case Report

A 79-year-old female was admitted with mild discomfort in the lower abdomen, anorexia and a left hydronephrosis. At cystoscopy a submucosal mass was found in the trigone of the bladder and proved pathologically to be a non-Hodgkin's malignant lymphoma (small lymphocytic) of the bladder. Careful radiological examination and lymph node biopsy showed no evidence of lymph node swelling and lymphocytic infiltration in any other part of the body. She has completed 4 courses of chemotherapy (doxorubicin, vincristine, cyclophosphamide and pred-

Late Perinephric Abscess Formation after Extracorporeal Shock Wave Lithotripsy

W. KOCHAKARN and K. RATANA-OLARN, *Division of Urology, Department of Surgery, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Case Report

A 58-year-old woman had a 1.3-cm stone in the right lower calix. Function was normal in both kidneys. Physical examination and routine investigations, including a blood coagulogram, were normal. Extracorporeal shock wave lithotripsy (ESWL) was performed in one session with the EDAP-LT₀₁ piezoelectric lithotripter at a power of 100%, 5 impulses/s and a treatment time of 68.15 min. The post-ESWL course was uneventful apart from haematuria for a few days; the patient received a 5-day course of trimethoprim/sulphamethoxazole. Plain X-ray showed no residual stones.

Six months later she developed fever with right flank pain. On admission a 10 × 10-cm mass was palpated in the right flank. Intravenous urography showed distortion of the right pelvicaliceal system (Fig.). A low echogenic area beneath the right kidney extending to the back was seen in the ultrasonogram. A computed tomography (CT) scan revealed a low density area extending from the right kidney to the back muscles.

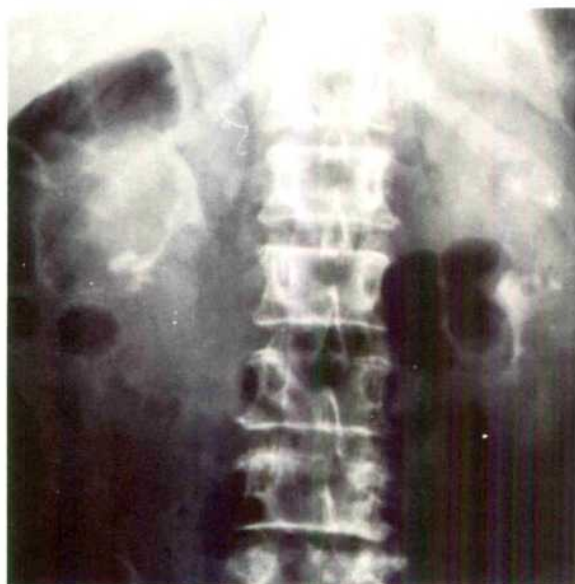


Fig. IVU 6 months after ESWL.

A right lumbar incision revealed a perinephric collection of approximately 800 ml of pus. After drainage, right nephrectomy was performed. Pathological examination showed a necrotic area in the mid portion of the kidney. Microscopic examination showed acute and chronic pyelonephritis. Pus culture revealed *Klebsiella ozaenae*.

Comment

The overall complications of ESWL are few but one of them is perinephric haematoma, with an incidence of 0.4% (Newman *et al.*, 1987). However, CT scans and magnetic resonance imaging after ESWL have indicated a much higher incidence of renal and perirenal haemorrhage (Rubin *et al.*, 1987). CT scans of 130 non-selected patients after lithotripsy with EDAP-LT₀₁ identified 5 (3.8%) subcapsular and 4 (3.1%) small parenchymal haematomas (Kim *et al.*, 1989). No mention was made of intrarenal abscess following ESWL. Our patient might have had a parenchymal injury with secondary infection which subsequently burst to form a perinephric collection of pus.

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Spontaneous Renocolic Fistula in Vesicoureteric Reflux

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Case Report

An 8-year-old boy was admitted with right-sided abdominal pain and a 2-year history of recurrent urinary tract infections.

Blood count and blood chemistry investigations were normal. Non-visualisation of the right kidney with a normal left kidney was demonstrated on IVU; a ^{99m}Tc-DMSA scan revealed no uptake in the right kidney and several hypoactive areas in the left kidney. A pre-operative diagnosis of renocolic fistula was based on voiding cystourethrography which showed bilateral vesicoureteric reflux on both sides, but the ascending and transverse portion of the colon was also visualised (Fig.).

The patient was explored through a right paramedian incision and right nephroureterectomy and colo-colostomy with resection of the involved colon were carried out. Histopathological examination revealed pyonephrosis and chronic inflammation in the colon. There was no evidence of tuberculosis or malignancy.

Comment

Fistulas between the urinary and alimentary tracts can occur in areas affected by chronic inflammation, necrosis or ischaemia; the most common sites for renal fistulas are the ascending and descending portion of the colon (Gibbons and Schmidt, 1965).

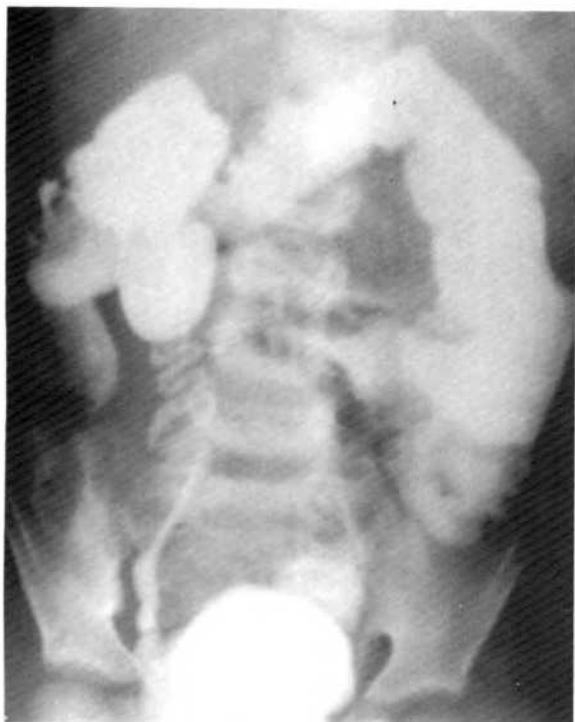


Fig. Voiding cystourethrography shows vesicoureteric reflux on both sides; the ascending and transverse portion of the colon is also visualised.

In our patient the cause was vesicoureteric reflux associated with recurrent urinary tract infection. The recommended treatment is nephrectomy of the non-functioning kidney and resection of the bowel involved (Hanafy, 1984; Mooreville *et al.*, 1988).

Acknowledgements

We thank S. Sargin and C. Tanyel for their assistance during surgery.

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Unusual Migration of a Ureteric Calculus

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Department of Urology, Northern General Hospital, Sheffield

Case Report

A 49-year-old woman presented with a history of renal colic. Intravenous urography confirmed the presence of a ureteric calculus obstructing the lower end of the right ureter (Fig. 1A). Extraction of the calculus was attempted, using the Dormia basket, but failed.

Within 4 weeks symptoms had recurred and an attempt was made to remove the stone with the ureteroscope. The ureter was dilated and the 14 F ureteroscope passed to the renal pelvis, but the stone was not visualised and we thought it had been extruded during ureteric dilatation. The patient's symptoms settled and an IVU showed the stone to be outside the ureter (Fig. 1B). A renogram confirmed normal function and excretion by both kidneys. The patient remained asymptomatic for 18 months, when again she developed right renal colic. An IVU showed the extruded calculus to be once again within the ureter (Fig. 1C). Shortly afterwards it was passed and the patient remains well with a normally functioning kidney.

Comment

Endoscopic removal of calculi in the lower ureter is now the preferred method of treatment, with a success rate of over 90% (Das *et al.*, 1988). Perforation of the ureter during the procedure without significant extravasation of urine or other sequelae is not uncommon and fragments of calculi often lie outside the ureter after such an event (Bishop *et al.*, 1987).

A whole ureteric calculus may be extruded (Tolley and Buist, 1986) but we cannot find a previous report of such a stone migrating back into the ureter. Patients are informed of the position of their extruded stone to prevent confusion should symptoms recur but, as this case illustrates, further migration should be considered.

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Fig. 1 Sequential intravenous urograms indicating the stone's position at each stage.

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Points of Technique

Coronal Haemostatic Suture for Partial Nephrectomy

F. S. HADDAD and PATTI A. FLINT, *Urology Section, Carl T. Hayden Veterans Administration Medical Center, Phoenix, USA*

Despite several new methods and techniques devised to establish haemostasis following partial nephrectomy, the most recent of which is a new dissecting instrument (Goldwassser *et al.*, 1986), one still encounters cases where the recommended techniques fail to control the bleeding. We found the following technique to be very effective in a patient in whom conventional methods—including the standard transverse sutures which tore through the capsule and the renal parenchyma—failed to control the bleeding.

After careful freeing and mobilisation of the kidney, its circulation is controlled by left thumb and index finger pressure on the hilar vessels, while the renal lesion is resected; if the pelvicaliceal system has been partially resected, it is repaired; finally a coronal circular suture is placed and tied around the cut end of the kidney (Fig.). This coronal suture holds well and results in immediate haemostasis.

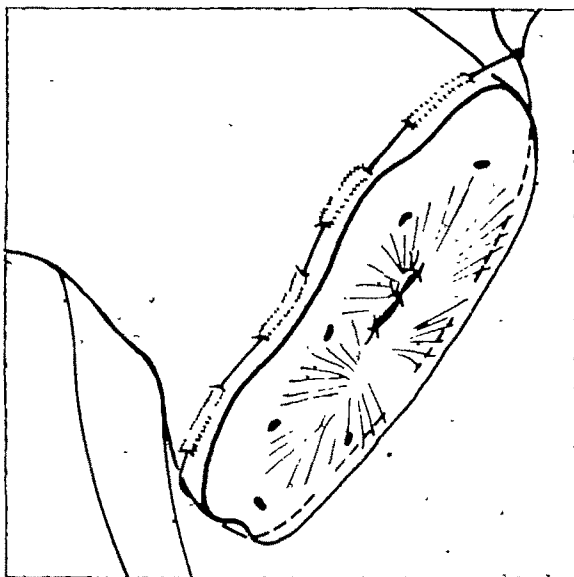


Fig. Coronal haemostatic suture in place, ready to be tied

This suture has been used before, not as a definitive haemostatic suture, but as a temporary measure while the major intrarenal blood vessels were individually ligated (Williams *et al.*, 1967).

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Badenoch's Pull-through Procedure in the Management of Urethrorectal Fistulae

P. B. SINGH, S. SARAF, A. KUNDU, P. K. KESARI and V. N. P. TRIPATHI, *Division of Urology, Department of Surgery, Institute of Medical Sciences, Varanasi, India*

Urethrorectal fistula resulting from iatrogenic trauma is a difficult urological problem and the many surgical procedures used in its management reveal the complexity of the disease and require extensive dissection and bowel interference.

We have used Badenoch's pull-through procedure in the management of a patient with urethrorectal fistula and suggest that it may provide a simpler alternative to the other methods.

Case Report

C.L., a 29-year-old male, had a posterior urethral stricture with urinary fistula in the thigh following fracture of the pelvis. Transpubic urethroplasty with excision of the fistulous tract was performed in December 1987. Post-operatively the patient developed a urinary leak through the rectum and he was discharged with a suprapubic cystostomy.

He was readmitted after 6 months for evaluation. The results of routine investigations were within normal limits. Retrograde urethrography revealed a complete block as the result of resticture. Voiding cystourethrography resulted in visualisation of the rectum (Fig.). A fistulous opening could be felt *per rectum* about 2½ cm from the anal margin. Cystoscopy revealed a complete block at the bulbo-membranous junction.

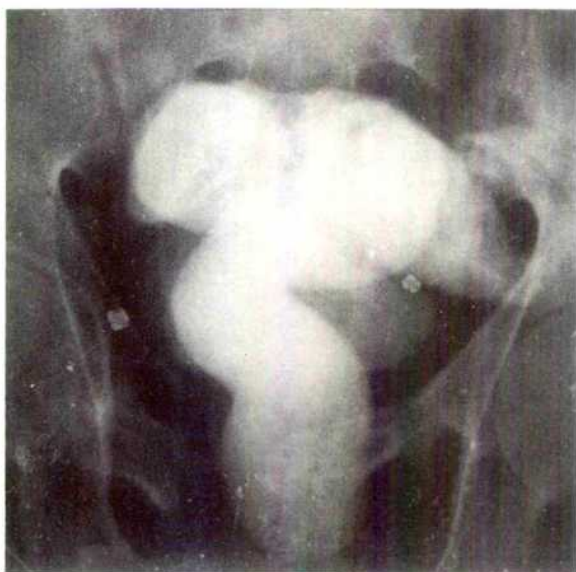


Fig. Voiding cystourethrogram visualising rectum.

In view of the urethrorectal fistula and the stricture, a Badenoch's pull-through procedure was done without disturbing the fistulous opening.

Recovery was uneventful and the patient voided normally, with no urinary leak through the rectum. Micturating, cystourethrography (MCU) 6 weeks post-operatively revealed a normal tract. Follow-up 1 year later has shown no complications.

Comment

Urethrorectal and vesicorectal fistulae are frequently the result of surgical trauma usually associated with perineal surgery. The diagnosis can often be made if the patient develops faecaluria, recurrent urinary tract infection or a urinary leak through the rectum post-operatively. The diagnosis can be confirmed by physical examination, careful rectal examination and X-ray techniques (particularly cystography and MCU) which will demonstrate rectal visualisation (Goodwin *et al.*, 1958).

Several surgical techniques have been proposed for the repair of rectourinary fistulae, including rectal pull-through (Young and Stone, 1917), direct exposure and repair through a perineal approach (Wilhelm, 1944; Goodwin *et al.*, 1958; Culp and Calhoon, 1964), repair through the intact dilated anal sphincter (Vose, 1949), closure of fistula posteriorly through a Kraskes incision (Benevente and Cassebaum, 1971) and transrectal repair through the divided sphincter (Kilpatrick and Mason, 1969; Talarico and Fernandes, 1969). In

recent years, Parks' method of closing rectourethral fistulae has become popular (Tiptaft *et al.*, 1983). In this method, after mobilizing the descending colon and sigmoid, the sigmoid is transected and after stripping mucosa and submucosa from the distal stump of rectum up to the white line, it is brought through the raw sleeve of the rectum and sutured.

Our patient had 2 problems—a stricture and a rectourethral fistula. It was decided to use Badenoch's pull-through procedure, which has the same effect on the fistulous tract as the role of sigmoid in Parks' operation.

It is suggested that Badenoch's pull-through procedure may be an effective alternative in the treatment of urethrorectal fistulae where the fistulous opening is obliterated by pulling up the normal urethra.

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An Appliance to Direct Urine Flow following Penile Amputation

C. L. GARBUTT, A.-M. GARDNER and N. E. DUDLEY,
Department of Surgery, John Radcliffe Hospital, Oxford

Penile amputation does not produce incontinence but it does lead to problems in directing the stream of urine. We describe an appliance, made from

materials readily available on a general surgical ward, which reduces this problem.

Case Report

A 78-year-old man presented with a 2-month history of penile swelling associated with a green, offensive discharge unresponsive to antibiotics. His past history included transurethral resection of the prostate and total hip replacement.

On examination he had a reddened, swollen penis with a purulent discharge. There was no lymphadenopathy. A dorsal slit biopsy confirmed moderately well differentiated invasive squamous cell carcinoma. He was treated by partial amputation of the penis, which left him with practically no residual stump. An appliance was made (Fig. 1) which helped him to direct the stream of urine. At follow-up he was using the appliance with great success, being able to stand and urinate normally.



Fig. 1



Fig. 2

Comment

The basic component was a 50-ml Plastipak syringe (Becton Dickinson, Dublin, Ireland) with the plunger removed. The wings of the syringe were bent back by heating with an electric hairdryer (Fig. 2). Some Stoma-hesive wafer (Squibb Surgicare, Twickenham) was moulded to the wings and 10 cm of oxygen link tubing attached to the end (Pennine Health Care, Derby). The appliance was used by holding the wings of the syringe in contact with the skin around the urethral orifice. After use it was rinsed with cold water. The estimated cost is £1. Thus this is a cheap and effective way of solving an uncommon but important problem.

Requests for reprints to: N. E. Dudley, Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Correspondence

Dear Sir,

Re The dangers of a long urological waiting list. M. C. Bishop. *Br. J. Urol.*, **65**, 433–440, 1990.

Mr Bishop concluded in his article that it is doubtful whether the delay in diagnosis or treatment of cryptorchidism seriously influences morbidity and mortality from this urological illness. He also contended that cryptorchidism is a congenital abnormality rather than an acquired effect, and that there is no increase in the risk of developing testicular malignancies amongst cryptorchid patients. These statements are incorrect and they are very misleading.

All cryptorchid patients within the first few months of life have normal testes with normal numbers of germ and Sertoli cells (Hadziselimovic. *Cryptorchidism: Management and Implication*. Berlin: Springer. 1987; Huff *et al. Eur. J. Pediatr.*, **146**, S25, 1987) and with a probability of typical fertility. However, the marked atrophy of the Leydig cells observed in this age group is caused by impaired gonadotrophin secretion; it is not the consequence of a congenital malformation (Hadziselimovic and Herzog. *J. Pediatr. Surg.*, **11**, 1–6, 1976; Gendrel *et al. Acta Endocrinol.*, **89**, 372–375, 1978; Baker *et al. Arch. Dis. Child.*, **63**, 1198–1202, 1988). Furthermore, boys with intra-abdominal testes have a 40 times greater risk of developing malignancies (Cromie. In Hadziselimovic. *Cryptorchidism: Management and Treatment*. Berlin: Springer. 1983) and carcinoma *in situ* was observed in 18% of the patients with intra-abdominal testes who were more than 12 years of age (Hadziselimovic *et al. Eur. J. Pediatr.*, **146**, 8–13, 1987).

Patients who have received either successful medical or surgical treatment have a significantly better chance of attaining normal fertility (Hadziselimovic and Herzog. *Hodenerkrankungen im Kindesalter*. Stuttgart: Hippokrates. 1990). In addition, early corrective surgery has been effective in preventing secondary testicular damage (Hadziselimovic. *Cryptorchidism: Management and Implication*. Berlin: Springer. 1983; Hadziselimovic and Herzog. *Hodenerkrankungen im Kindesalter*. Stuttgart: Hippokrates. 1990. Mininberg *et al. J. Urol.*, **123**, 782–787, 1982) and it significantly diminishes the risk of patients developing a seminoma later (Halme *et al. Br. J. Urol.*, **64**, 78–81, 1989).

The overall tone of the section on cryptorchidism

is defeatist and harmful for those with less knowledge of the current literature on this subject.

Yours faithfully,

F. Hadziselimovic
Department of Pediatrics, Basler Kinderspital,
Basel, Switzerland.

Reply by M. C. Bishop. I do not agree that a positive approach to very early orchiopexy is yet justified by the evidence. Cryptorchid testes are often small and associated with herniae and a selection of more profound congenital genitourinary abnormalities. For example, the frequent finding of adnexal anomalies will obviously affect ultimate sperm transport adversely even if germ cell development can be improved by early surgery; 36 to 56% of unilateral and 74% of bilateral undescended testes are said to show severe epididymal abnormalities (Mininberg. *Eur. J. Pediatr.*, **146**, S28–30, 1987; Marshall and Shermata. *J. Urol.*, **121**, 341–344, 1979).

There is a considerable body of evidence showing progressive cytological, histological and biochemical abnormality of the cryptorchid testis with increasing age before treatment. The drawbacks of such work are demonstrated well in the investigation quoted (Huff *et al. Eur. J. Pediatr.*, **146**, S25, 1987). There is considerable variation in the data. This may well reflect on interobserver variability in the clinical diagnosis of cryptorchidism as well as genuine heterogeneity. Clearly, different studies are likely to describe varying properties of different conditions described as cryptorchidism. It is still uncertain whether such changes are reversible and Professor Hadziselimovic would be the first to acknowledge that normal appearances very early in life do not guarantee normal intrinsic potential for germ cell development and, even less so, normal function. Despite his admirable optimism, there is no hard evidence that early surgery prevents such changes. The study he quotes by Mininberg *et al. (J. Urol.*, **123**, 782–787, 1982) is typically misleading in assuming orchiopexy at age 1 year, when changes are minimal, will prevent severe collagen deposition and germ cell loss apparent in later years. In any case, this particular study is flawed by the very small numbers investigated.

Better evidence on reversibility might come from comparison of testicular biopsies performed pre- and post-operatively in undescended and descended testes. In an early study, Canlorbe *et al. (Ann.*

Pediatr. (Paris), 13, 270–275, 1966) showed that improvement was related entirely to histology at the time of operation and not to age when it was performed. There is more evidence for intrinsic gonadal defect as opposed to environmental factors from defective spermatogenesis described in many studies on the contralateral descended testis (Hez-mall and Lipshultz. *Urol. Clin. North Am.*, 9, 361–369, 1982).

In general, British and American surgeons do not believe that medical treatment of cryptorchidism is ever effective. Clearly the chances of normal fertility from such treatment of the retractile testis are likely to be excellent.

I certainly did not say that there was no risk of malignancy in undescended testes. The increased risk in the abdominal testis is indisputable and I did not even mention this. However, the computed risk for the ectopic and canalicular testis will certainly vary with the incidence of undescended testes in the population. The study quoted was merely one example where the risk was minimal. Professor Hadziselimovic states that early corrective surgery has been effective in diminishing the risk of a patient developing a seminoma. This is also misleading as the reference quoted (Halme *et al. Br. J. Urol.*, 64, 78–91, 1989) does not describe a reduction in risk of tumour development, merely the effect of orchiopexy on the type of tumour occurring after operation. In any case, surgery in this study was anything but early (up to 15 years!).

I would suggest that none of my comments was misplaced or misleading. The justification for early orchiopexy awaits the results of a prospective controlled trial from a small number of reliable units where the clinical diagnosis of cryptorchidism can be fully substantiated and properly subdivided. Surgery will need to be standardised and performed by only a small number of skilled operators. Careful follow-up will be required. It will take at least another generation before we know.

Dear Sir,

re Skin bridge—a complication of paediatric circumcision. U. V. Sathaye *et al. Br. J. Urol.*, 66, 214, 1990.

In their discussion, the authors propose that these skin bridges are the result of inadequate separation of the inner preputial epithelium from the glans at the time of circumcision. We have seen these skin

bridges on numerous occasions. Our impression, however, is that they are the result of post-operative adhesions following circumcision. The cut skin edges that are fused together by a Gomco clamp adhere post-operatively to the glans penis. In addition, the raw surfaces of the remaining inner prepuce and glans can also easily re-adhere following their blunt separation during circumcision. Diligent care is needed to prevent their occurrence. Unfortunately, the post-operative management is not often stressed to the family. This same problem can develop in the uncircumcised child who undergoes forcible retraction of the prepuce prior to its natural separation.

If the prepuce is not completely retracted at the time of circumcision, this area should gradually separate with the passage of time. We believe that it is the traumatised area that readheres which is more apt to form a dense fibrous adhesion. We recently evaluated a group of neonates undergoing circumcision and found that 10% had some degree of adhesion at the coronal margin on their 1-month well baby check. Most of these will resolve spontaneously and only a small percentage of circumcised patients will form a dense adhesion that will develop into a skin bridge. We see on average only 1 to 2 patients annually with a skin bridge. Proper instruction on care of the circumcised patient could further reduce even this small number.

Yours faithfully,

M. L. Ritchey and D. A. Bloom
Section of Urology, Department of Surgery, University of Michigan, Ann Arbor, USA.

Dear Sir,

re Gamma-seminoproteins—a new tumour marker in prostatic cancer? U. Maier and R. Simak. *Br. J. Urol.*, 65, 509–512, 1990.

We read with interest the above contribution. The following comments are made in order to clarify an annoying misunderstanding. Koyanagi (*Igaku Kenkyu*, 44, 69–88, 1974) purified from human seminal plasma a protein which he designated gamma-seminoprotein. Wang *et al. Invest. Urol.*, 17, 159–163, 1979) likewise from human seminal plasma purified a protein which was called prostate-specific antigen. Since 1987, according to independ-

ent work by several laboratories (Watt *et al. Proc. Natl. Acad. Sci. USA*, **83**, 3166–3170, 1986; Akiyama *et al. FEBS Lett.*, **225**, 168–172, 1987; Lundwall and Lilja. *FEBS Lett.*, **214**, 317–322, 1987; Schaller *et al. Eur. J. Biochem.*, **170**, 111–120, 1987), it is known that gamma-seminoprotein and prostate-specific antigen are one and the same protein. The question raised by Maier and Simak: gamma-seminoprotein: a new marker in prostatic cancer? can therefore be easily answered. No, because gamma-seminoprotein is prostate-specific antigen and prostate-specific antigen is an established tumour marker in prostatic cancer.

I cannot judge how many colleagues will be misled and/or confused by the contribution of Maier and Simak. However, since the paper obviously was reviewed and passed this examination the fact that gamma-seminoprotein and prostate-specific antigen are one and the same protein might not be as known to the researchers working in this field as it should be. Furthermore, there remains the puzzling result presented by Maier and Simak that the test for assaying gamma-seminoprotein (GSM-Chugai, Chugai Pharmaceutical Corporation Ltd) apparently does not have the same specificity for prostate-specific antigen as an established prostate-specific antigen assay employed by the authors in this study.

Yours faithfully,

K. H. Scheit

Department of Molecular Biology, Max-Planck-Institut für Biophysikalische Chemie, Göttingen, Germany.

Dear Sir,

re A pitfall in the diagnosis of supernumerary kidney. A. K. Yousef *et al. Br. J. Urol.*, **67**, 100, 1991.

We were interested to read the above report of a single supernumerary kidney. We described a case of 2 supernumerary kidneys in a premature neonate of 38 weeks' gestation who lived for 1 hour 20 minutes (L. H. Zondek and T. Zondek. *Ann. Paediatr.*, **203**, 46–58, 1964). This rare case has not been mentioned in recent publications on the subject and we believe it deserves renewed attention owing to its unique nature.

It is of historical interest that Hyrtl (*Ost. Med. Wochenschr.*, 40–53, 965–967, 1841) mentions with

some scepticism Gemma (1575) and de Marchettis (1765) as having reported a case with 5 kidneys. In Hyrtl's own case the supernumerary third kidney was about half the size of a goose's egg and was present on the left side, at the entrance of the pelvic cavity. In our case one supernumerary kidney was lying on each side above the normal kidney, the latter being found in their normal positions. Each kidney had its own pelvis and ureter. The supernumerary kidneys were almost cystic and had only a narrow rim containing both mature and immature glomeruli and tubules as well as a few islets resembling primitive fetal cartilaginous tissue, which is not an uncommon finding in cystic and hypoplastic kidneys (J. A. Bigler and W. P. Killingsworth. *Arch Pathol.*, **47**, 487, 1949). There was also infiltration of cells resembling lymphocytes in various areas, as has been described by J. E. Morison (*Fetal and Neonatal Pathology*. Second edition. P. 369. London: Butterworths. 1963) in his account of hypoplasia of the kidney. Both testes were lying in the scrotum and showed some degree of underdevelopment. Both epididymes were underdeveloped and showed only weak secretion, a most unusual finding at this stage of gestation. Associated congenital malformations included a ventricular septal defect and deformity of the left radius and left ulna. The only other description of 2 supernumerary kidneys of which we are aware is that of A. P. Pinter *et al. (J. Urol.*, **127**, 119–120, 1982).

Yours faithfully,

L. H. Zondek and T. Zondek

Institute of Obstetrics and Gynaecology, Hammersmith Hospital, London.

Dear Sir,

re Foley catheter balloon puncture and the risk of free fragment formation. J. M. Chrisp and J. N. Nacey. *Br. J. Urol.*, **66**, 500–502, 1990.

We are particularly interested in this study which demonstrated convincingly the significant risk (27.3%) of separation of free fragments upon balloon rupture. The authors rightly concluded by making a plea for routine cystoscopic examination in the event of rupture of the Foley balloon, either spontaneously or during attempts at removing a retained Foley catheter.

The report began with a seemingly exhaustive list of techniques available for the removal of a retained Foley, but omitted the one reported by us (W. D. Ng *et al.* *Br. J. Surg.*, **74**, 1067, 1987). Incidentally, our method is the only one using cystoscopy.

For years now, it has been our practice to remove a retained Foley catheter by gently sliding a well lubricated 10F or 13F paediatric cystourethroscope alongside the catheter under direct vision, while the latter is put under traction, until the balloon comes into view. The balloon is then punctured by the inner needle of a flexible oesophageal variceal injector inserted via the instrument channel. Indeed, on 2 occasions sizeable fragments of the balloon were detected and retrieved cystoscopically at the same sitting. Our clinical experience lends support to the author's recommendation, which has been based solely on *in vitro* studies.

Yours faithfully,

J. W. D. Ng and A. Y. T. Chan
Surgical B Unit, Princess Margaret Hospital, Hong Kong.

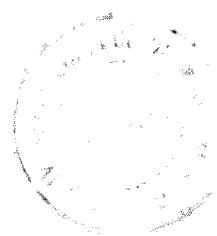
Dear Sir,

re Ureteric substitution with Boari bladder flap.
H. G. Motiwala *et al.* *Br. J. Urol.*, **66**, 369-371, 1990.

It is accepted that the Boari flap is an excellent reconstructive urological procedure to bridge the gap caused by loss of the lower ureter. However, the extended use of the Boari flap to bridge more proximal ureteric defects is gaining importance owing to its good results. Thus we successfully repaired a long ureteric stricture (post-traumatic) extending from the pelviureteric junction to the vesicoureteric junction by using a Boari flap. Its use, therefore, need not be restricted to lower third defects. The prerequisite is that pre-operative hydrodistension of the bladder should be performed in gradually increasing amounts to ensure that one has an adequate length of Boari flap at the time of open surgery.

Yours faithfully,

S. Khanna
Department of Urology, Ganga Ram Hospital,
New Delhi 60, India.



Notices

British Association of Urological Surgeons

Autumn Meeting: Royal Surrey County Hospital, Guildford. 4 and 5 October 1991

The Day Meeting of the Association on 5 October will be preceded by a post-graduate education session on 4 October, when the topic will be "Can Urologists Manage?"

Further information from: BAUS Secretariat, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21-26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Surgery in the Third World

Sir Ian Todd, past President RCSI, is anxious to build up a list of surgeons in all specialties from the United Kingdom and Northern Ireland (active or recently retired consultant, or higher surgical trainee) who would like to spend some time working and teaching in a third world country.

In most cases accommodation and subsistence are provided and in some air fares also. Periods abroad vary from 1 month upwards but 3 to 6 months are usually preferred.

Please write to Sir Ian Todd, KBE, FRCS, care of the Overseas Doctors Training Scheme Office at the Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Diary

1991

- September 15–18 64th National Congress of the Italian Society of Urology in Trieste, Italy. Contact: Professor Giorgio Carmignani, President of the Congress, Ospedale di Cattinara Strada di Fiume, 447 34149 Trieste, Italy.
- September 16–19 Second Beijing International Symposium on Recent Advances in Urology, Beijing, China. Contact: Gu Fang-liu, Institute of Urology, Beijing Medical University, 1 Da Hong Luo Chang, West District, Beijing 100034, China.
- September 23–25 16th Annual Meeting of the International Urogynaecology Association, Sydney, Australia. Contact: Conference Secretariat, International Professional Travel P/L, Suite 103, 135 Macquarie Street, Sydney, NSW 2000, Australia.
- September 26–27 Annual Paediatric Urology Course, Cambridge. Contact: Mr R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
- October 3–5 Prostate Cancer and Urothelial Cancer; Controversies in Diagnosis and Treatment, Orlando, Florida. Contact: Imedex U.S.A. 1060 Cambridge Square, Suite D, Alpharetta, Georgia, U.S.A.
- October 3–5 Annual Meeting of Swiss Society of Urology, Geneva, Switzerland. Contact: Prof. Dr D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.
- October 4–5 Autumn Meeting, Royal Surrey County Hospital, Guildford. Contact: BAUS Office.
- October 9–12 1st International Congress, Dutch Urological Association (NVU), Rotterdam. Contact: NVU/PACIOU Congress Secretariat, Department of Urology, Erasmus University Rotterdam/Academic Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam. The Netherlands.
- October 10–12 International Continence Society, 21st Annual Meeting, Hannover. Contact: Guus Kramer, Chairman ICS, Department of Urology, Hannover Medical School, P.O. Box 610180, 3000 Hannover 61, Germany.
- October 18–19 Surgical Treatment of Prostatic Cancer: Comparison of Techniques. Milan, Italy. Contact: Dr F. Gaboardi, Divisione di Urologia, Ospedale Fatebenefratelli ed Oftalmico, C.so Porta Nuova 23, 20121 Milan, Italy. Tel. 0039-2-636443.
- October 20–November 4 Royal College of Surgeons of England Joint Meetings in Pakistan and India. Contact: Craig Duncan, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London, WC2A 3PN.
- November 15–16 Third Biennial Asia-Pacific Meeting on Impotence, Taipei, Taiwan, R.O.C. Contact: Third Biennial Asia-Pacific Meeting on Impotence, c/o Taiwan Conference Management Co. Ltd, P.O. Box 68–439, 6F–3, 102 Chung Shan N. Road, Sec. 2, Taipei, Taiwan, R.O.C.
- 22-November 21 Controversies in the Management of Prostatic Cancer, St Bartholomew's Hospital. Contact: Dr A. Jelliffe, NETRHA, 40 Eastbourne Terrace, London, W2 3QR. Tel: 071 262 8011.

November 22–23 International Pelviureteric Junction Obstruction Symposium, Stratford-on-Avon. Contact: Mr P. Shridhar, Department of Urology, George Eliot Hospital, Nuneaton CV10 7DJ.

1992

January 10 Final date for submission of abstracts for the 1992 BAUS Annual Meeting.

March 8–13 19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.

March 19–21 Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.

April 9–11 6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.

May 6–8 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.

May 10–14 American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.

May 24–28 Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.

June 10–12 Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.

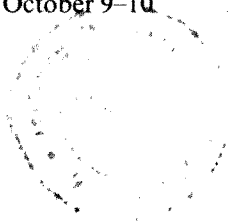
June 22–25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.

June 23–26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.

July 22–25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.

August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.

October 9–10 BAUS Autumn Meeting, Harrogate. Contact BAUS Office.



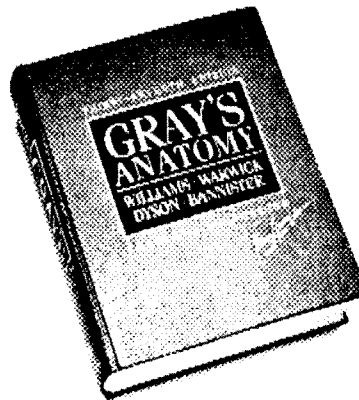
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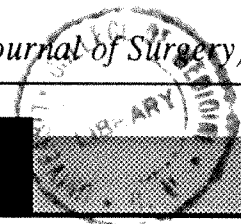
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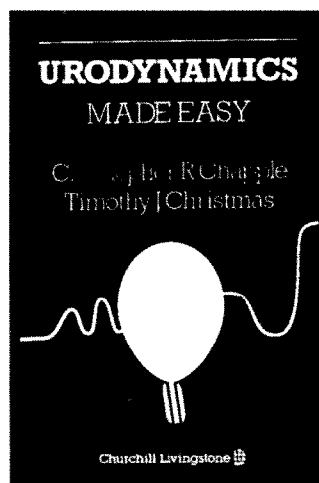
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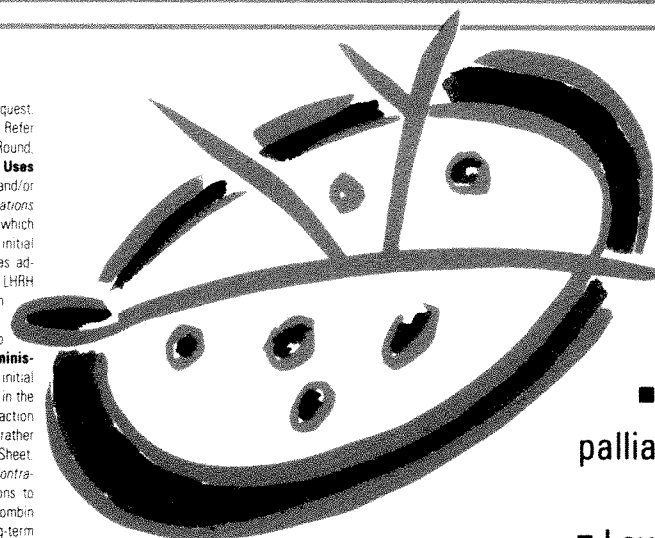
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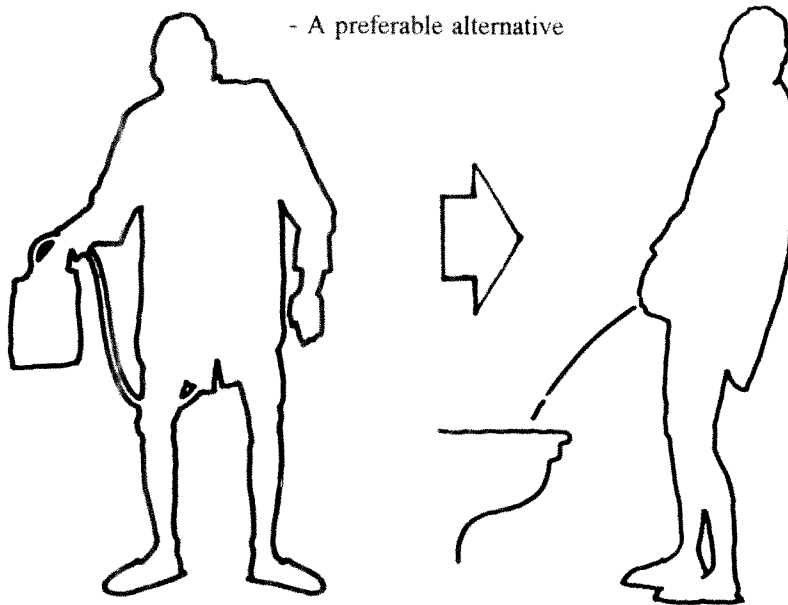
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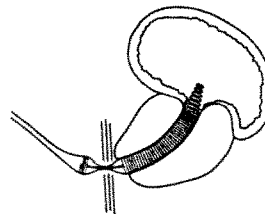
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REVIEW

The Investigation of Impotence

W. J. JEFFCOATE

City Hospital, Nottingham

Normal Erection

An erection occurs when blood flows into the corpora cavernosa (and spongiosum and glans) at flow rates of approximately 100 ml/min—sufficient to raise intracorporeal pressure above a critical level. When intracorporeal pressure exceeds 80 mmHg, emissary veins are compressed against the inner aspect of the tunica albuginea and venous drainage is blocked (Lue *et al.*, 1986). Detumescence occurs when reduced arterial flow results in a fall in intracorporeal pressure, allowing venous blood to escape. However, it is likely that other pathways may be involved, including both active vasoconstriction and closure of arteriolar-venular shunts (Lue and Tanagho, 1987; Krane *et al.*, 1989).

The control of these processes must be complex, but very little is known of the details. Increased flow down the pudendal arteries requires arterial dilatation and will be aided by increased cardiac output resulting from tachycardia. The arterial blood will be redistributed within the corpora as a result of arteriolar relaxation and, probably, closure of arteriolar-venular anastomoses. These depend on smooth muscle relaxation and contraction induced by any one of a number of transmitters: the vasodilator released from the terminals of the sympathetic and parasympathetic erectile nerves (currently thought to be vasoactive intestinal polypeptide (VIP)), vasodilator peptides derived from the cells of the endothelium and media of the vessel wall (such as endothelium derived relaxing factor (EDRF) and calcitonin gene related peptide (CGRP)), as well as circulating catecholamines and other hormones. For these transmitters to work, the smooth muscles in the walls of the small blood vessels must themselves be capable of responding by relaxation or contraction, and this is dependent

on the normal distribution of Na^+ , K^+ , Ca^{++} and other ions across the cell membrane. Finally, the whole process can be inhibited by activation of the sympathetic α -adrenergic anti-erectile pathway which results in reduced arterial inflow: erections are inhibited at times of stress.

It follows that there are numerous reasons for erection failure, and it is more than likely that in many men the problem is partial dysfunction of two or more systems rather than the complete failure of one. Thus a man with some atheromatous narrowing of the pelvic vessels may be more susceptible to factors precipitating "psychogenic" impotence, while the erection of a man with some degree of autonomic dysfunction, from either diabetes or from aging, may be more dependent on reflex stimulation and may therefore be imperfect if he has associated peripheral sensory neuropathy. There are exceptions, of course, such as impotence secondary to trauma to the pelvis, or spinal transection, or overt endocrine or psychosexual dysfunction, but they are uncommon.

Against this background of scientific ignorance and multi-faceted pathogenesis, one must question the value of clinical tests. Do they really help decide on the cause of a man's impotence? Even if they are diagnostically precise, does it matter? Does knowledge of assumed cause modify either management or outcome?

History and Examination

A simple history will help to establish that the man's problem is really erection failure, and it will also help to define obvious psychosocial disharmony. Classical diagnostic features of the history—such as intermittence, preservation of morning erections and loss of libido—are not very helpful (Slag *et al.*, 1983). However, routine clinical examination should exclude abnormalities of size

and shape of the penis, as well as obvious hypogonadism. History and examination should also help to define other problems, including diabetes, alcohol abuse, cardiac disease, peripheral vascular disease and peripheral neuropathy. Drugs can cause impotence—particularly those used in the treatment of hypertension. Other preparations can also be implicated: oestrogens and antiandrogens (including digoxin, cimetidine and spironolactone), and drugs which elevate serum prolactin (metoclopramide, domperidone and phenothiazines).

Alcohol and Diabetes

While the presence of other organic problems should be noted, they should not be assumed automatically to be the sole cause of the problem. After all, antihypertensives are only prescribed for people with hypertension, *i.e.* for those with significant vascular disease, and the prescription of other drugs may be for an illness which itself may modify either organic sexual function or the man's self-esteem. It should be remembered that people with impotence who drink alcohol to excess may have one because of the other, or the other because of one. The personality which seeks companionship by downing large volumes of liquid in a public house is not usually the sort which is well adapted to a mature and stable sexual relationship. The same may be true also of the professional who comes home late from work to pour himself several glasses of whisky, and to collapse into the comfort of mental and physical detumescence. The main value of defining alcohol abuse in someone with impotence is to promote its treatment, rather than to define a specific cause for the presenting complaint.

While it is stressed that the commonest reason for alcohol and impotence being linked is psychosocial, there remain a number of possible metabolic mechanisms by which excessive ethanol may "equivocate with lechery" and provoke sexual dysfunction in some people. The problem of the porter who bemoaned the link in Macbeth was somnolence induced by intoxication, rather than impotence, but it is worth noting that acute ethanol intoxication does lead to a rise in serum prolactin concentration (Jeffcoate *et al.*, 1981). On the other hand, those with cirrhosis have an increase in plasma oestrone, and testosterone concentrations may be reduced by testicular atrophy. However, one of the strongest pieces of evidence incriminating ethanol came from the important prospective

study of McCulloch *et al.* (1984). They found that insulin-dependent diabetics who drank to excess (more than 40 units each week) were more likely to develop impotence over the succeeding 5 years than those who drank less ($P < 0.0001$). It is possible that ethanol-induced changes in the metabolism of sodium, magnesium and calcium result in critical dysfunction of the neurovascular reflexes necessary for shunting of blood into the corpora cavernosa. A similar mechanism may explain the impotence which occurs with thiazides.

When a man who presents with impotence is found to have diabetes, it is equally tempting to assume that it is the cause, but the assumption may not be justified. A diabetic is just as likely to have undiagnosed hypogonadism as a non-diabetic, and the prevalence of psychogenic impotence in diabetes has been estimated to be between 9 and 19% (Lehman and Jacobs, 1983; McCulloch *et al.*, 1984; Miccoli *et al.*, 1987). Moreover, it is not established for certain that impotence is more common in diabetes: that would require accurate information on the occurrence of impotence in the non-diabetic population, and none is available. Such evidence as there is suggests that problems of erection occur in 34% of male medical out-patients (Slag *et al.*, 1983) and up to 16% of healthy men in their early thirties (Frank *et al.*, 1978). The available evidence in diabetics (those who attend hospital clinics) suggests that between 23 and 50% (Kolodny *et al.*, 1974) have impotence. In the important study by McCulloch *et al.* (1980) the overall prevalence was 35%, which is almost exactly the same as that reported by Slag *et al.* (1983).

The history and examination should be followed by some simple investigations to help define what may not be clinically obvious: elevated γ GT, blood glucose, prolactin and LH, or reduced testosterone. These measurements should not be omitted—even when there is another apparent cause—but the dilemma which faces the clinician is whether or not he should do more. There are many other investigations which could be done and they are of varying sophistication, cost and inconvenience. It is clearly important that they should be employed by those units pursuing research in the field, but do they help in routine practice?

There are tests of "unaided" erection and tests of pharmacologically stimulated erection. There are tests of arterial supply and of venous drainage. Finally, there are indirect tests—tests of somatic sensory and motor function—and tests of autonomic neuropathy. One or more are variously described as the hallmark or gold standard, but

readers should remember that those who write reviews will usually have a specific research interest in the investigation of impotence, and are likely to recommend tests with which they are most familiar.

NPT and VSS

Tests of "unaided" erection include recording of nocturnal penile tumescence (NPT) and of erections induced by watching erotic videos (VSS). There are many ways in which the quality of the erection occurring in these tests can be recorded, e.g. manually, by photograph, mercury strain gauge, snap gauge, plethysmography. If a man is observed to get a good erection by such means, it is reasonable to assume that his arterial supply is good enough to raise intracorporeal pressure and block venous drainage. The converse is not, however, true: failure to achieve an erection does not necessarily indicate that the man's problem is "organic": an abnormal response to NPT and/or VSS has been reported in 25% of men with psychogenic impotence (Melman *et al.*, 1988) as well as in 20% of potent normal controls (Schiavi and Fisher, 1982). If the test is not done well and the environment is not conducive to relaxation, erections may be inhibited by the sympathetic anti-erectile pathway. Some other methodological problems have been listed by Karachan (1988). To be done properly they require considerable investment of staff and space, and work at unsocial hours.

Papaverine

Intracorporeal injection of the vasodilator, papaverine (or of prostaglandin E, PGE) will induce an erection if the arterial supply is good enough. The action of papaverine appears to be complex, for an independent action in reducing venous drainage has also been demonstrated (Lue *et al.*, 1986), even though the details of the mechanism are unknown. A small dose should be given at first for fear of causing priapism—and the risk is greatest in those with marked clinical neuropathy. However, men with poor vascular supply may need 45 or 60 mg, even combined with an α -blocking agent such as phentolamine. Allen and Brendler (1988) have found that 88% of men with predominantly psychogenic impotence, 100% of those with neurogenic impotence, and 90% with relatively mild vascular disease will respond to intracorporeal papaverine. The test is therefore less useful than NPT and VSS at differentiating psychogenic impotence from other causes, but has the single great advantage of

nearly always demonstrating whether an erection is possible at all. It may be diagnostically imprecise, but at least it shows that something can be done.

Ultrasound and Arteriography

Measurement of systolic blood pressure in the dorsal artery of the penis is easily done and the penile:brachial index (PBI) should normally exceed 0.6. The test can be made more complicated by attempting to demonstrate a pelvic "steal" phenomenon by asking the person to exercise his pelvis for a few minutes (Goldstein *et al.*, 1982). Nevertheless, false positive results can be obtained because sympathetic inhibition of arterial blood flow can result in low pressures in "psychogenic" impotence, as well as in normal people who are not sufficiently relaxed. In one study, 11 of 42 men with PBI <0.6 subsequently returned to normal sexual activity, suggesting that their problem was predominantly psychogenic (Melman *et al.*, 1988). Although Puppo *et al.* (1988a) found a good correlation between PBI and the dose of papaverine required to induce an erection, others have found the correlation between the results of Doppler studies and the response to papaverine to be poor (Mellinger *et al.*, 1987; Lakin and Montague, 1989). More sophisticated analysis of unidirectional and bidirectional wave form analysis by Doppler ultrasound (Lue *et al.*, 1985), alone or in combination with intracavernosal papaverine, will only be employed by those with a specialist interest in the field, and they will be aware that interpretation of the results requires caution. In routine clinical practice, measurement of penile artery systolic pressure, and of PBI, is of little use.

Arterial blood supply can also be assessed by contrast angiography. This is expensive and invasive and should only be done in those in whom reconstructive vascular surgery is likely to be beneficial. While some report success rates for arterial surgery of up to 75% (Virag *et al.*, 1981; Bennett, 1988), many feel that a successful outcome is effectively confined to young men with traumatic interruption of the pelvic vessels. Those suitable for arterial surgery probably represent less than 1% of all men presenting with impotence (Puppo *et al.*, 1988b).

Venous Leak?

In the last 10 years attention has focused on an alternative vascular cause of erection failure. Thus it has been argued that an otherwise adequate

arterial supply will be insufficient if the veins are abnormally leaky. Two main types of test have been described to demonstrate this "venous leak", usually called cavernometry and cavernography. Phallometry and phallography are linguistically more correct terms, even if anatomically more vague.

The principle of cavernometry is the attempted induction of a passive erection by the infusion of saline into the corpora. The average flow required to induce an erection is 120 ml/min, but there is great individual variation (Newman and Reiss, 1984). Flow rates are less when cavernometry is performed after the intracorporeal injection of papaverine (pharmacocavernometry), presumably because the drug reduces venous outflow (Lue *et al.*, 1986; Wespes *et al.*, 1986; Dickinson and Pryor, 1989). When it is impossible to raise intracorporeal pressure above 80 mmHg, or to induce an erection with flows of 80 ml/min during pharmacocavernometry (250 ml/min if papaverine is not used), or to maintain one with an infusion of 10 ml/min (40 ml/min without papaverine), it is assumed that the person has abnormal venous drainage. Nothing is known of the structural and functional abnormality which may lead to an acquired venous leak but it may be an abnormality of venoconstriction—if active venoconstriction normally occurs. Alternatively, there may be increased arteriolar-venular shunting—analogueous to the abnormal circulation which occurs in the neuropathic diabetic foot.

However, it is just as likely that the main reason for venous leak is arterial: if blood does not enter the penis sufficiently fast to raise intracorporeal pressure—either because of atheroma, or because the sympathetic anti-erectile pathway is activated, as in psychogenic impotence—then the emissary veins will not be compressed. Thus the results of both cavernometry and cavernography will suggest an abnormality of the veins, when the problem may in fact rest with the arteries. This has been highlighted by DePalma *et al.* (1989), who found false positive results in tests of venous leak in men with arteriopathy. False positive results have also been reported in psychogenic impotence (Desai and Gingell, 1988) as well as in 12% of normally potent controls (Newman and Reiss, 1984).

Tests of Somatic and Autonomic Neuropathy

The last types of test which are described in the investigation of impotence are indirect tests. These are tests which define the occurrence of associated abnormalities which may, or may not, be causally

related to the failure of erection. They include tests of peripheral sensory and peripheral motor function. Their diagnostic specificity is always open to question since the occurrence of 2 problems in the same individual does not prove a causal relation between them. There seems little extra evidence to justify the use of tests of sensory and motor function in the perineal region, such as the bulbocavernosus reflex latency test and pudendal sensory threshold testing. Not only are they diagnostically imprecise because of great overlap between "neuropathic" and "non-neuropathic" groups (Desai *et al.*, 1988), they must also be very unpleasant to have done. Tests of autonomic neuropathy, such as measurement of loss of sinus arrhythmia (*i.e.* vagal denervation of the heart), are non-invasive and simple if the apparatus is available, but are very indirect and therefore contribute little to a definite diagnosis of cause.

The Place of Investigation in Management

Current strategies for the routine management of impotence are simple (Jeffcoate, 1986). The first tasks are to confirm that the problem is truly one of failed erection, to exclude hypogonadism, and to identify relevant drug therapy and the occurrence of associated disease. Once this has been done, the treatment options should be discussed (including the safety and medico-legal aspects of papaverine administration). The man should then be offered a trial of papaverine (or PGE) in increasing dose. Whatever the cause of the problem, he may or may not get an erection. If he does not, and there is a history of pelvic trauma, he should be considered for arteriography. Otherwise he should be offered vacuum devices or implants—if he wants them—irrespective of the presumed cause of his problem. Erections may improve following psychotherapy, and counselling may certainly help a couple adjust to their problem even if potency does not improve. However, the results of psychotherapy are not overwhelmingly good (McCulloch *et al.*, 1986) and if a man (with or without his partner) does not benefit from it, or does not wish to have his/their privacy dissected, it seems reasonable to offer prostheses—irrespective of the presumed cause.

More intensive investigations can be undertaken, but not in the hope that they will identify the "cause" of the impotence. They will not do so, partly because the results are always open to varied interpretation and partly because we simply do not know enough of the factors involved to hope that any test will help us to identify them. In the light of

current knowledge, there are only 2 reasons for doing tests. The first is clinical satisfaction, enabling the clinician to derive a more complete picture of the man's clinical state, and this in itself will help explanation and counselling. The second is research. We still have much to learn.

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Hyperoxaluria in Patients with Recurrent Calcium Oxalate Calculi: Dietary and Other Risk Factors

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Summary—The presence of mild hyperoxaluria in recurrent calcium oxalate stone formers is controversial. The aim of this study was to identify recurrent stone formers with mild hyperoxaluria and to classify them further by assessing their response to a low oxalate diet. In addition, the prevalence of other risk factors for stone formation in this group of patients was investigated. A total of 207 consecutive patients with recurrent renal calculi were screened and 40 (19%) were found to have mild hyperoxaluria. Of these, 18 (45%) responded to dietary oxalate restriction by normalising their urinary oxalate. The remaining 22 patients were classified as having idiopathic hyperoxaluria and were subdivided into those in whom urinary oxalate excretion was consistently elevated in all specimens measured and those in whom the elevation was intermittent in nature. Dietary oxalate restriction had a partially beneficial effect in lowering oxalate excretion in the patients with persistent hyperoxaluria. No difference in urinary oxalate excretion was found after dietary restriction in the patients with intermittent hyperoxaluria. Other risk factors, including dietary, absorptive and renal hypercalciuria and hypocitraturia, were documented, the prevalence of which (65%) was not significantly different from that (62.5%) found in 40 age- and sex-matched calcium stone formers without hyperoxaluria. The prevalence of hyperuricosuria was significantly greater in patients with hyperoxaluria when compared with stone controls. Further studies are required to elucidate the underlying mechanisms of hyperoxaluria in recurrent stone formers.

Oxalate, an end product of ascorbate and glyoxylic acid metabolism, is derived from dietary and endogenous sources (Broadus and Thier, 1979). Primary hyperoxaluria is a rare genetic disorder of glyoxylic acid metabolism characterised by excessively high oxalate excretion ($>1000 \mu\text{mol}/24 \text{ h}$), calcium oxalate nephrolithiasis, nephrocalcinosis and eventual rapid progression to end stage renal failure (Watts, 1988).

We have defined mild hyperoxaluria as urinary oxalate excretion $>350 \mu\text{mol}/24 \text{ h}$ but without systemic consequences. Mild hyperoxaluria has been associated with diets low in calcium, high in oxalate or those containing excessive amounts of ascorbate. It has also been reported consequent to the steatorrhea which has followed small bowel disease, ileal resection and jejunoileal resection

(Smith *et al.*, 1972; Dobbins and Binder, 1977; Coe, 1983).

The occurrence and pathogenesis of mild hyperoxaluria (MHO) in idiopathic calcium stone disease are controversial. Urinary oxalate has been variably reported to be normal (Bach *et al.*, 1979; Galosy *et al.*, 1980) or raised (Marshall *et al.*, 1972; Robertson *et al.*, 1978, 1980).

The hyperoxaluria has been attributed to intestinal hyperabsorption or increased renal clearance of oxalate (Pinto *et al.*, 1974; Hodgkinson, 1978; Marangella *et al.*, 1982).

The aims of this study were to identify recurrent stone formers with hyperoxaluria, to classify them further by assessing their response to a low oxalate diet and to determine dietary and other metabolic risk factors. The association and prevalence of these other abnormalities have not been adequately documented in patients with MHO. Risk factors

were considered to be hypercalciuria induced by excessive calcium and/or sodium ingestion which normalised on dietary manipulation; absorptive or renal hypercalciuria as assessed by abnormal calcium: creatinine ratios (Pak *et al.*, 1975) and hypocitraturia (< 2.1 mmol/24 h) (Laminski *et al.*, 1990). In addition, hyperuricosuria (defined as > 4.4 mmol/24 h) was considered to be a risk factor.

Patients and Methods

A group of 207 consecutive patients with recurrent calculi attending the metabolic stone clinic at the Johannesburg Hospital were screened for hyperoxaluria. A detailed dietary assessment of calcium, oxalate and protein ingestion was obtained by our dietician. Dietary calcium, oxalate and protein excess was defined as > 1000 mg/day, > 200 mg/day and > 1.25 g/kg/day respectively. Forty patients with MHO were identified and classified as follows: dietary hyperoxaluria (DHO, $n=18$) defined as patients whose urinary oxalate returned to normal on a low oxalate diet; idiopathic persistent hyperoxaluria (PHO, $n=10$), patients whose urinary oxalate was persistently raised and, although it decreased, failed to return to normal on diet; idiopathic intermittent hyperoxaluria (IHO, $n=12$), patients whose urinary oxalate was intermittently raised, diet having no effect.

Two control groups were chosen: 40 age- and sex-matched recurrent calcium stone formers without hyperoxaluria formed the stone control group (SC) and 56 normal controls without stones formed the normal controls (NC). Patients with gout, purely infective stones, obstructive uropathy or renal tubular acidosis were excluded. No patient had any gastrointestinal pathology. In addition, none of the patients was on sodium cellulose phosphate, thiazides or ingesting large amounts of vitamin C.

Standard laboratory methods were used to measure 24-h urinary sodium, calcium, phosphorus, creatinine and uric acid. Urinary citrate was measured enzymatically using the Boehringer Mannheim citric acid kit (Warty *et al.*, 1984). Urinary oxalate was measured enzymatically using the Boehringer Mannheim oxalic acid kit (Cannon *et al.*, 1975). Calcium: creatinine ratios were performed according to the method of Pak *et al.* (1975). The tests were performed on the patient's usual diet and repeated on a low oxalate diet; 24-h urine collections were carried out in each patient from 4 to 8 times. Renal calculi were analysed using a standard qualitative wet chemical technique.

Statistical evaluations were made using paired or non-paired Student's *t* tests, chi-squares (χ^2) with Fisher Exact corrections and correlation coefficients where indicated.

Results

Of the 207 patients studied, 40 (19.3%) had MHO. There was a significantly greater oxalate intake in the DHO and PHO groups than in the SC or NC groups ($P < 0.03$). There was no significant difference in oxalate intake in the IHO group compared with either group of controls (Table 1). Urinary oxalate excretion in $\mu\text{mol}/24$ h was significantly increased in all groups of patients with hyperoxaluria, *i.e.* DHO, PHO or IHO versus SC and NC ($P < 0.001$) (Table 1). The PHO group had the highest urinary oxalate excretion, and although their urinary oxalate decreased when placed on a low oxalate diet, it still remained higher than that of any of the other groups ($572.93 \pm 132.68 - 445.05 \pm 88.70$) ($P < 0.03$) (Table 1). This presumably reflected the fact that the initial dietary intake of oxalate was higher in these patients. When placed on dietary oxalate restriction, only DHO patients lowered their oxalate excretion to within the normal range ($420 \pm 71.5 - 261.44 \pm 27.71$) ($P < 0.0005$). In the IHO group, oxalate restriction had no effect on oxalate excretion ($344.71 \pm 32.51 - 329.00 \pm 35.27$) (NS). The Figure demonstrates the intermittency and lack of correlation with diet of the hyperoxaluria in 2 of these patients. No difference was found between oxalate intake or urinary oxalate excretion in the SC versus NC groups.

There were no significant differences in the prevalence of dietary abnormalities, hypocitraturia or abnormal calcium: creatinine ratios between the stone formers with MHO or the stone controls (Table 2). Hyperuricosuria was found in 12 patients with MHO but only in 3 stone controls ($\chi^2 = 6.45$, $P < 0.001$).

There were no significant differences in the number of calculi passed per year between the MHO patients, *i.e.* DHO, idiopathic hyperoxaluria (PHO and IHO) and the SC group (1.15 ± 0.95 , 0.88 ± 0.72 and 0.94 ± 1.10 respectively).

In 11 patients with DHO 18 calculi were analysed; 61% of these were calcium oxalate, 17% were calcium phosphate and 22% contained other mixtures. Twenty-three calculi were analysed in 13 patients with idiopathic hyperoxaluria (PHO and IHO); 39% of these were calcium oxalate, 39% were calcium phosphate and 23% contained other mix-

Table 1 Daily Oxalate Intake and 24-h Urinary Oxalate Excretion

Group	No.	Oxalate intake (mg/24 h)	Urinary oxalate ($\mu\text{mol}/24\text{ h}$)	
			Usual diet	Oxalate restriction
DHO	18	224.96* ± 117.08	420.90‡ ± 71.50	261.44* ± 27.71
IHO	12	132.58 ± 90.78	344.71‡ ± 32.51	329.00‡ ± 35.27
PHO	10	231.44* ± 99.02	572.93‡ ± 132.68	445.05‡ ± 88.70
SC	40	145.38 ± 107.23	215.39 ± 70.32	ND
NC	56	141.20 ± 105.39	208.60 ± 89.93	ND

Values expressed as means $\pm$ SD. Statistical differences from controls using non-paired *t* test are shown, * $P < 0.03$, ‡ $P < 0.001$.

DHO = dietary hyperoxaluria. IHO = intermittent idiopathic hyperoxaluria. PHO = persistent idiopathic hyperoxaluria. SC = stone controls. NC = normal controls. ND = not done.

tures. Twenty-four patients in the SC group had 32 stones analysed, of which 72% contained calcium oxalate, 16% were calcium phosphate and 13% contained other mixtures. All patients who formed a calcium phosphate calculus had also formed 1 or more calcium oxalate calculi.

There was no difference in the prevalence of hypertension or family history of renal calculi in the stone patients with hyperoxaluria and those

without. There was an increased prevalence of diabetes mellitus in the stone formers with MHO (8 patients) compared with the stone controls (1 patient) ($\chi^2 = 6.13$, $P < 0.014$). Only 1 patient with intermittent and 2 with persistent hyperoxaluria had an increased daily protein intake. There was no correlation between protein intake and oxalate excretion in patients with MHO ($r = -0.01$, NS).

Discussion

This study has permitted the definition of 2 groups of patients with recurrent calcium renal calculi and mild hyperoxaluria, namely those whose condition was related solely to diet and those with mild idiopathic hyperoxaluria. The latter group could be further subdivided into patients with either persistent or intermittent hyperoxaluria. The PHO patients had a mild dietary component, without urinary oxalate ever completely returning to normal, whereas diet had no effect on the group with IHO. Thus 19% of recurrent stone formers screened had hyperoxaluria and in 45% of these, dietary oxalate restriction reversed the defect.

The mechanisms of hyperoxaluria in the idiopathic group are not clear. None of the patients had any gastrointestinal abnormalities. MHO is unlikely to be due to a pyridoxine deficiency, which has been reported to cause hyperoxaluria in both man and animals (Yendt, 1983). None of the symptoms of pyridoxine deficiency was present in

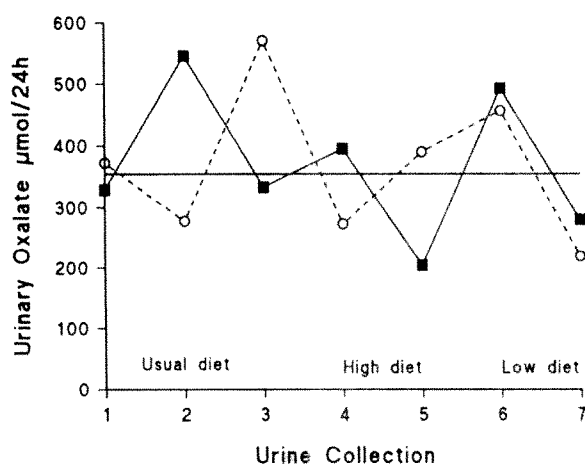


Fig. Pattern of urinary oxalate excretion in 2 patients with intermittent hyperoxaluria on usual, high and low oxalate diets. Twenty-four hour urine collections 1, 2 and 3 were on usual diet, 4 and 5 on high oxalate diet and 6 and 7 on low oxalate diet. ■—■ = patient PS. ○- - -○ = patient LT.

Table 2 Other Risk Factors in Patients with Hyperoxaluria

Group	NMA*	Abnormal Ca/creat		Hypocitraturia	Hyperuricosuria
		R=renal	A=absorp		
DHO	7 (39)		1A (6)	9 (50)	4 (22)
Idio HO	5 (23)	4R (18)	4A (18)	7 (32)	8 (36)
SC	15 (38)	3R (8)	6A (15)	17 (43)	3 (8)

Expressed as no. of patients (% patients).

*NMA: No metabolic abnormality, but includes reversible dietary excess, i.e. increased calcium and/or sodium intake.

DHO = dietary hyperoxaluria. Idio HO = idiopathic hyperoxaluria (includes intermittent and persistent hyperoxaluria) SC = stone controls.

these patients. Previous investigations in patients with MHO have shown increased xanthuric acid excretion after tryptophan loading which was corrected by pyridoxine, which is indicative of pyridoxine deficiency (Gershoff and Prien, 1960). Since high doses of tryptophan and unreliable methods for xanthuric acid measurement were employed, however, the interpretation of these results is in doubt (Yendt and Cohanin, 1988). Some investigators have suggested that MHO is secondary to absorptive hypercalciuria. Hyperabsorption of calcium results in less calcium to bind oxalate in the gut, so that more oxalate is available for colonic absorption (Marangella *et al.*, 1982). Four of our patients with idiopathic hyperoxaluria had this disorder but 18 did not. Furthermore, 6 of the stone controls also had absorptive hypercalciuria without hyperoxaluria, so this explanation seems unlikely. It would seem possible that renal hypercalciuria could also result in hyperoxaluria. Patients with this disorder leak calcium from the kidney, resulting in parathyroid hormone activation, increased formation of $1,25(\text{OH})_2\text{D}_3$ and increased absorption of calcium from the gut, theoretically permitting an increase in oxalate absorption. However, although 4 of the patients with MHO had renal hypercalciuria, 14 did not; 3 of the stone controls also had renal hypercalciuria without hyperoxaluria, so making this explanation unlikely.

A high intake of animal protein has been implicated as a cause of mild hyperoxaluria, particularly intermittent hyperoxaluria (Yendt and Cohanin, 1988). Protein intake was increased in only 3/22 patients with idiopathic and in 1/12 with intermittent hyperoxaluria. In addition, no correlation between protein intake and urinary oxalate was found in either the PHO or the IHO patients.

Gill and Rose (1986) described an entity which they called "mild metabolic hyperoxaluria" in which there are modest increases in both urinary

oxalate and glycolate. This disorder appears to be a different entity from classical primary hyperoxaluria because of the negative family history, onset in adult life, occurrence predominantly in males and the intermittent nature in some patients. Our idiopathic hyperoxaluric patients may have an underlying metabolic abnormality similar to that described by Gill and Rose (1986). However, we did not measure urinary glycolate. The aetiology of this condition is unknown but may result from slightly decreased activity of the peroxisomal enzyme alanine: glyoxylate transaminase, which is lacking in patients with primary Type I hyperoxaluria. Erythrocyte oxalate flux in these patients may also be abnormal, reflecting an increased oxalate uptake. This abnormality has been reported by Baggio *et al.* (1986) in idiopathic calcium oxalate nephrolithiasis. However, the association of this disorder with elevated urinary oxalate excretion was not reported and so needs to be studied in this group of patients.

Although renal and absorptive hypercalciuria and hypocitraturia could not be incriminated in the causation of the hyperoxaluria, these abnormalities were present in 25/40 patients (63%) and so presented additional risk factors for stone formation. Of interest is the fact that these additional risk factors were present in a similar proportion in the stone controls (26/40, 65%). Hyperuricosuria, which has been shown to salt out oxalate, resulting in calcium oxalate precipitation even at normal levels of urinary oxalate, would constitute an important risk factor in these patients (Grover *et al.*, 1990). Twelve of our patients with mild hyperoxaluria had hyperuricosuria, a significantly increased prevalence ($P < 0.001$) compared with the stone controls, thus greatly increasing their risk of stone formation. In fact, hyperoxaluria as the sole metabolic abnormality was present in only 5/22 patients (23%) with idiopathic hyperoxaluria.

It is noteworthy that a proportion of calculi

analysed consisted of calcium phosphate without oxalate. Thus the formation of such calculi should not necessarily preclude the search for possible MHO. The reason for this is obscure. None of our patients had renal tubular acidosis, hyperparathyroidism or urinary tract infections.

In conclusion, 19% of patients with recurrent calcium stone nephrolithiasis had mild hyperoxaluria defined as urinary oxalate $> 350 \mu\text{mol}/24 \text{ h}$. In 45% of these dietary manipulation had a beneficial effect. The mechanism of idiopathic hyperoxaluria is unclear. This study suggests that hyperuricosuria might be an important additional risk factor for calcium oxalate nephrolithiasis. However, the exact mechanism by which this occurs has not been addressed in this report.

Further investigations, in which glycolate excretion and oxalate flux are measured, are in progress in our MHO patients and it is hoped that further light will be shed on the mechanism of this interesting and common condition.

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Renal Function after Partial Nephrectomy with the Nd-YAG Laser

Experimental Study in Piglets

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Summary—Twelve partial nephrectomies were performed in 12 piglets using either the combination (contact and non-contact) Nd:YAG laser technique or a steel scalpel. Additional haemostasis was attempted with ligatures. The renal artery was not clamped and renal cooling was not attempted. Total nephrectomy was performed on the contralateral side. Serum creatinine and urea levels were measured, and ^{99m}Tc -DTPA renography was performed pre-operatively and 1 and 2 weeks post-operatively. One week post-operatively the mean serum creatinine level was 35% higher than the pre-operative level in the laser group and 30% higher in the steel scalpel group. Two weeks post-operatively the respective differences were 34 and 24%. The mean urea level 1 week after operation was 50% higher than the pre-operative level in the laser group and 17% higher in the steel scalpel group. Two weeks post-operatively the respective differences were 38% in the laser group and 20% in the steel scalpel group. The mean DTPA disappearance rate was 34% lower 1 week after operation in the laser group and 23% lower in the steel scalpel group when compared with the pre-operative state. Two weeks post-operatively the respective changes were 48 and 25%. These data indicate that there is no significant difference in renal function when the Nd:YAG combination laser technique is used in partial nephrectomy as compared with the steel scalpel.

The use of partial nephrectomy in the management of renal carcinoma is increasing. The main complications in partial nephrectomy have been related to haemorrhage and urinary fistulas. Both CO_2 and non-contact Nd:YAG lasers have been used in experimental studies with acceptable results (Barzilay *et al.*, 1982; Benderev and Schaeffer, 1985). However, there have been only a few reports concerning the effect of laser energy on renal function. Benderev and Schaeffer (1985) used a non-contact Nd:YAG laser with a 100 W power output in canine partial nephrectomy and reported acceptable impairment of renal function. One month post-operatively the serum creatinine levels were 66% higher than the pre-operative values. The contact laser tips enable the use of significantly

lower energy outputs in laser surgery, thus minimizing the damage to adjacent tissues (Daikuzono and Joffe, 1985).

The purpose of the present study was to evaluate renal function in the partially resected kidney when using the Nd:YAG combination (contact and non-contact) laser technique. To enable a better comparison to be made of the function of the resected kidneys in the 2 treatment groups, contralateral nephrectomy was performed at the same time. To our knowledge, this is the first report where renography has been used to evaluate the effect of the laser technique on renal function.

Materials and Methods

Twelve partial nephrectomies were performed in 12 piglets weighing 11 to 17 kg (mean 14). The

animals were anaesthetised with intramuscular ketamine hydrochloride 25 mg/kg and intravenous pentobarbital sodium 30 mg/kg. Ringer's lactate (500 ml) was administered intravenously during the procedure. The animals were intubated and connected to a mechanical ventilator (Manley) and ventilated using oxygen and nitrous oxide.

The kidneys were exposed through a midline abdominal incision. To improve monitoring of the effect of the 2 operative methods on the resected kidneys, total nephrectomy was done first on the left side. Partial nephrectomy was then performed on the right side with a laser scalpel (6 piglets) or with a steel scalpel (6 piglets). The renal vessels were not occluded during the procedure and renal cooling was not attempted. The lower pole guillotine resection was performed at the junction of the mid and lower thirds of the kidney.

A contact Nd:YAG laser SLT CL 60 (1.06 μ m wave length; Surgical Laser Technologies, Pa, USA) with a 12 W power setting was used in a continuous wave mode. The laser fibre was 2.2 mm in diameter and the contact tip 1.2 mm in diameter, 19 mm long and frosted (type ERP 12, SLT).

The guillotine resection with the laser scalpel was done by a gentle slow motion through the cortex and medulla with the tip perpendicular to the tissue surface. After laser resection, additional haemorrhage was coagulated using the non-contact technique with a 30 W power setting and with the 2.2 mm fibre 0.5 cm distant from the target. If the haemorrhage persisted, ligation was performed with 4/0 polyglycolic acid (PGA) sutures. In the steel scalpel group all bleeding vessels were ligated with 4/0 PGA sutures. The collecting system was closed with continuous 4/0 PGA sutures. No drains were used. The abdominal incision was closed in 2 layers with 2/0 PGA continuous sutures. The serum creatinine and urea levels were measured, and ^{99m}Tc -DTPA renography was performed pre-operatively and 1 and 2 weeks post-operatively.

Imaging

The piglets were imaged dynamically for 30 min using 10-s collection frames in a supine position from a posterior-anterior view; a Siemens Rota gamma camera was equipped with a general purpose high resolution parallel hole collimator (140 keV; 20% window). The data were analysed using a PDP-11 computer with Gamma 11/40 software.

The intravenously administered radiotracer was Tc- ^{99m} -diethylenaminepentaacetic acid (DTPA;

Solco-DTPA, Solco Ltd, Basel, Switzerland) and the dose was 1.0 mCi (37 MBq).

Computer analysis

The DTPA disappearance rate was determined using the region of interest (ROI) analysis of dynamic gamma images; the disappearance ROI was the upper body. In measuring the DTPA clearance the weight, length and haematocrit of the piglet were taken into account. A blood sample was taken from the subclavian vein 20 min after injection of the tracer; the radioactivity of 1 ml blood was measured using a well-type gamma counter for the clearance determination. The dynamic curves for the kidneys were obtained using the ROI analysis; for the disappearance rate calculations, blood pool correction and background correction were made by lining using the ROI method in the heart and spleen areas respectively (Tamminen *et al.*, 1978).

Blood samples

The DTPA disappearance rate was also determined during 6 dynamic studies taking blood samples before and 1, 2, 3, 5, 10, 15, 25, 40, 60 and 120 min after injecting ^{99m}Tc -DTPA (reliability of the method). The radioactivity of the blood samples was measured using a gamma counter (LKB 1282 Compugamma, Wallac, Turku, Finland). There was excellent correlation between the measured DTPA disappearance from the blood and the DTPA disappearance calculated from the gamma images using the ROI analysis ($r=0.97$, $n=6$).

Nuclear medicine

The dynamic curves (DTPA renograms) and gamma images were interpreted by a nuclear physician (K.J.A.K.) with no knowledge of the piglet's operative history. The calculations based on the ROI analysis were carried out independently by nuclear physicians and surgeons, and repeated analyses were also performed using different selection criteria for the definition of the ROIs; no statistically significant differences (2-way analysis of variance) were observed (validity of the method).

The piglets were sacrificed 2 weeks post-operatively. A histological specimen was taken from the resection line for haematoxylin and eosin staining.

Statistical analysis

The results are presented as mean $\pm$ standard error of mean (SEM). The Wilcoxon signed rank test was used in the statistical calculations.

Results

Creatinine. The mean serum creatinine level 1 week post-operatively was 35% higher than the pre-operative value in the laser group and 30% higher in the steel scalpel group (Table 1). One creatinine sample was omitted at 1 week's analysis in the steel scalpel group because of ileus, and a high creatinine value (167 $\mu\text{mol/l}$) was related to the dehydration of the animal. Two weeks after the operation the respective figures were 34% in the laser group and 24% in the steel scalpel group.

Table 1 Serum Creatinine Values ($\mu\text{mol/l}$) Pre-operatively and 1 and 2 Weeks after Partial Nephrectomy ($n=6$) (mean $\pm$ SEM). Wilcoxon signed rank test

	Pre-operative	1 week	2 weeks
Laser	91 $\pm$ 6	123 $\pm$ 6	122 $\pm$ 6
Steel scalpel	88 $\pm$ 3	114 $\pm$ 3*	109 $\pm$ 6
		$P=0.6858$	$P=0.173$
		* $n=5$	

Urea. The mean serum urea level 1 week post-operatively was 50% higher than the pre-operative value in the laser group and 17% higher in the steel scalpel group (Table 2). Two weeks post-operatively the respective changes were 38% in the laser group and 20% in the steel scalpel group. Two urea samples in the laser group were omitted from the analysis, since the animal was found to have pyohydronephrosis and ureteric obstruction, and high serum urea values at 1 and 2 weeks (7.3 and 8.9 mmol/l) were related to urinary obstruction. One urea sample in the steel scalpel group was omitted at 1 week's analysis due to ileus and dehydration (serum urea 18.1 mmol/l).

Table 2 Serum Urea Values (mmol/l) Pre-operatively and 1 and 2 Weeks after Partial Nephrectomy ($n=6$) (mean $\pm$ SEM). Wilcoxon signed rank test

	Pre-operative	1 week	2 weeks
Laser	2.6 $\pm$ 0.2	3.9 $\pm$ 0.2*	3.6 $\pm$ 0.5*
Steel scalpel	3.0 $\pm$ 0.5	3.5 $\pm$ 0.7*	3.6 $\pm$ 0.3
		$P=0.6858$	$P=0.8927$
		* $n=5$.	

DTPA disappearance rate. The mean $^{99\text{m}}\text{Tc}$ -DTPA disappearance rate was 34% lower in the laser group and 23% lower in the steel scalpel group 1 week after operation when compared with the pre-

operative values (Table 3). Two weeks after the operation the respective changes were 48% in the laser group and 25% in the steel group.

Table 3 $^{99\text{m}}\text{Tc}$ -DTPA Disappearance Rate (%/min) Pre-operatively and 1 and 2 Weeks after Partial Nephrectomy ($n=6$) (mean $\pm$ SEM). Wilcoxon signed rank test

	Pre-operative	1 week	2 weeks
Laser	1.00 $\pm$ 0.06	0.66 $\pm$ 0.10	0.52 $\pm$ 0.09
Steel scalpel	0.97 $\pm$ 0.09	0.75 $\pm$ 0.06	0.73 $\pm$ 0.06
		$P=0.6002$	$P=0.0747$

DTPA clearance. One week post-operatively, the mean DTPA clearance rate was 35% lower than the pre-operative value in the laser group and 8% lower in the steel scalpel group (Table 4). Two weeks after the operation the respective changes were 46% in the laser group and 22% in the steel scalpel group.

Table 4 DTPA Clearance Rate (ml/s) Pre-operatively and 1 and 2 Weeks after Partial Nephrectomy ($n=6$) (mean $\pm$ SEM). Wilcoxon signed rank test

	Pre-operative	1 week	2 weeks
Laser	0.54 $\pm$ 0.04	0.35 $\pm$ 0.05	0.29 $\pm$ 0.05
Steel scalpel	0.51 $\pm$ 0.07	0.47 $\pm$ 0.07	0.40 $\pm$ 0.07
		$P=0.173$	$P=0.14$

Histology. The histological sections were analysed in 10 piglets (5 in each group). The degree of necrosis and tissue damage was minimal and was similar in both groups. The thickness of the fibrotic zone was measured in 8 piglets and was <1.2 mm in both groups. The inflammatory reaction was severe in 3 kidneys (1 in the laser group, 2 in the steel scalpel group), moderate in 3 (1 in the laser group, 2 in the steel scalpel group), and mild in 4 (3 in the laser group, 1 in the steel scalpel group).

Discussion

The major problem in partial nephrectomy is bleeding which cannot be controlled by electrocoagulation, since it causes extensive destruction of the renal parenchyma and delayed healing of the resection surface. Although a CO_2 laser has been used in experimental studies with acceptable results (Barzilay *et al.*, 1982), its use is limited because of its inability to penetrate water or blood, which

complicates working in an area where there is significant blood loss (Foster *et al.*, 1988). Benderev and Schaeffer (1985) used a non-contact Nd:YAG laser with a 100 W power output in canine partial nephrectomy and reported "acceptable impairment of renal function". However, 1 month post-operatively the serum creatinine levels were 66% higher than the pre-operative values. The renal artery was occluded with a non-crushing clamp and the kidney was cooled with a normal saline ice-slush. A control group was not included in the study. The collecting system was not closed and 2 of the dogs had urinary extravasation, which could be a reason for the elevated serum creatinine values. In the present study, renal artery occlusion and renal cooling were not used and the collecting system was closed. The 2-week post-operative serum creatinine levels were 34% higher than the pre-operative values in the laser group (24% higher in the steel scalpel group). During the 2-week follow-up period there was no improvement in renal function. Kidney function measured with different parameters was at the same level 1 and 2 weeks post-operatively.

The contact Nd:YAG laser has been reported to have excellent haemostatic and cutting properties, even when there has been heavy bleeding, with minimal tissue damage and necrosis (Foster *et al.*, 1988). Benderev and Schaeffer (1985) reported that the total depth of necrosis ranged from 4 mm in the cortex to 7 mm in the medulla when using the non-contact Nd:YAG method. Landau *et al.* (1987) used a contact Nd:YAG laser with a cone-shaped tip and reported 2.7 mm as the maximal depth of tissue destruction. Johnson *et al.* (1988) used a variety of delivery systems with the Nd:YAG laser in partial nephrectomy in dogs and found maximal acute renal damage up to 1.8 mm. With the frosted tips a portion of the energy is scattered diffusely from the roughened lateral sides of the probe, allowing better coagulating properties (Foster *et al.*, 1988). When frosted tips with a 12 W power setting and non-contact coagulation with a 30 W setting were used in the present study, tissue necrosis was <1.2 mm. Histologically there was no difference between the groups.

When the left nephrectomy and the right partial nephrectomy were performed, the loss of renal parenchyma was estimated at 65 to 70%. The reduction in renal function in the steel scalpel group was related to the loss of renal parenchyma, but in the laser group there was additional thermal injury. Renal function tended to be more reduced in the laser group, but no statistically significant difference was found.

Benderev *et al.* (1987) found that clamping the renal artery significantly reduced the depth and width of laser damage when compared with the perfused kidney. In the present study the renal artery was not clamped and renal cooling was not attempted. It is obvious that renal cooling and clamping the renal pedicle would minimise the laser-induced thermal injury to the renal parenchyma.

The present results indicate that there is no significant difference in post-operative renal function between the Nd:YAG combination technique and the steel scalpel in partial nephrectomy in the pig. It is concluded that partial nephrectomy is technically feasible with the combination Nd:YAG method and further clinical studies appear warranted.

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Pyonephrosis and Renal Abscess Associated with Kidney Tumours

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Summary—Whilst the diagnosis of pyonephrosis and renal abscess is fairly easy, the source of obstruction and infection is an important indicator of treatment. The association of kidney tumours with these inflammatory manifestations has not previously been emphasised. Reviewing our cases of pyonephrosis and renal abscesses, we report 4 patients with concomitant tumours of the kidney and discuss their management.

Pyonephrosis is the end stage of an obstructed and severely infected kidney which becomes functionless and filled with pus.

Renal abscess is an inflammatory collection within the renal parenchyma and may extend into both perinephric and paranephric spaces.

The patients history, the clinical findings and the laboratory results are usually diagnostic of pyonephrosis and renal abscess (Godec *et al.*, 1981). Sometimes the inflammatory process occurs in a kidney that contains tumour.

We present 4 patients with pyonephrosis or renal abscess in kidneys with concomitant tumours which were found incidentally.

Patients and Methods

We reviewed the records of 17 patients with pyonephrosis and 8 with renal abscess treated over a 10-year period. During this time 34 patients with renal carcinoma and 9 with transitional cell carcinoma of the renal pelvis were also treated and their records were reviewed.

Results

Thirteen patients with pyonephrosis had obstructive nephrolithiasis. The other 4 had no significant history of previous disease within the genitourinary

tract. All were given antibiotics intravenously. Five patients with lithiasis were managed successfully by draining the infected pelvis with a ureteric catheter; the others underwent nephrectomy.

One patient, a 72-year-old woman with a history of breast cancer surgically treated 2 years previously, was found, at operation, to have a renal carcinoma in the heavily infected kidney. Her IVU had revealed a functionless right kidney with disappearance of the psoas muscle outline, characteristic of a collection in the retroperitoneal space (Fig. 1).

The second patient, a 68-year-old man with a history of dull right flank pain 2 weeks previously, presented with a fever $>40^{\circ}\text{C}$ for 3 days. The most important findings were significant leucocytosis and slight bilirubinaemia. CT scan showed a collection of pus within the right non-functioning kidney (Fig. 2). He underwent nephrectomy for pyonephrosis. The kidney was removed intact and pathological examination revealed a transitional cell carcinoma of the renal pelvis, causing obstruction.

The third patient, a 56-year-old man with a history of haematuria, had an abscess in the upper pole of the kidney, extending into the perinephric space (Fig. 3).

The fourth patient, a 63-year-old man, had an abscess in the upper half of the kidney (Fig. 4) while the rest of the parenchyma was almost normal.



Fig. 1 IVU. Non-functioning right kidney and disappearance of the right psoas outline.

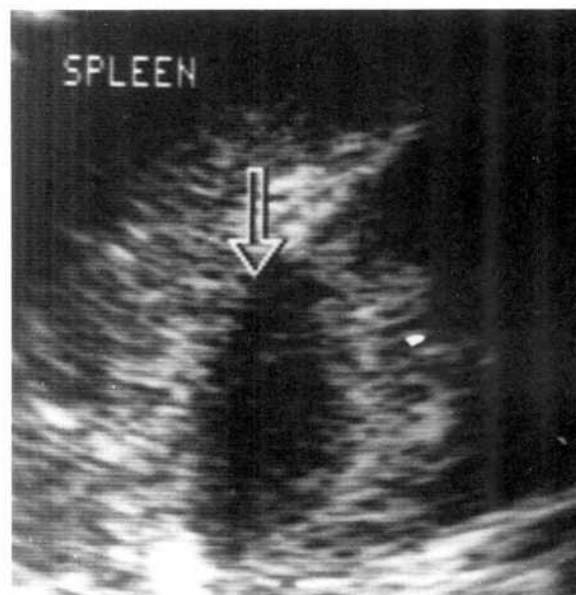


Fig. 3 Ultrasonic scan shows abscess in left upper pole of the kidney.



Fig. 2 CT scan demonstrates collection of pus within the right kidney.

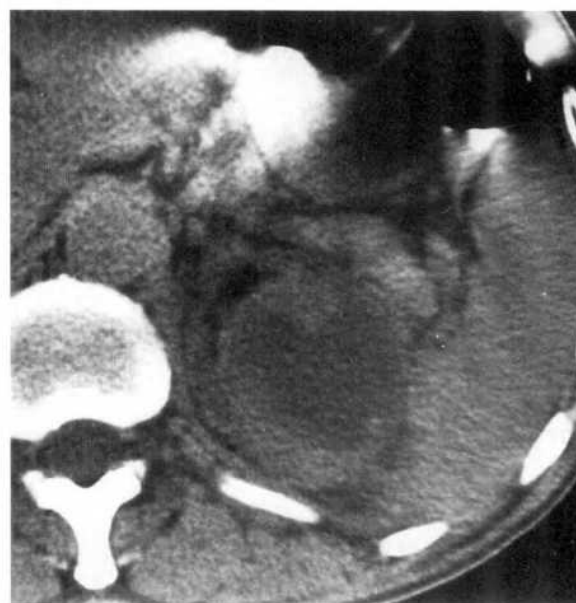


Fig. 4 CT with oral and intravenous contrast media. Abscess with enhanced walls in left upper pole.

Table Details of Patients

Patient no	Sex, Age	History	Side	Type of tumour	Organism	Culture
1	F, 72	Breast cancer	R	Renal cancer	<i>E. coli</i>	Urine pos Blood neg.
2	M, 68	Flank pain	R	Transitional cell cancer	<i>E. coli</i>	Urine pos. Blood neg.
3	M, 56	Haematuria	L	Renal cancer	<i>S. aureus</i> (coag. +)	Urine pos. Blood pos.
4	M, 63	—	L	Renal cancer	<i>E. coli</i> <i>B. fragilis</i>	Urine neg. Blood pos

Histopathologically, the third and fourth patients proved to have renal carcinoma (Table).

Discussion

Patients with pyonephrosis do not respond to antibiotics alone, so that relief of obstruction and drainage of pus are required to prevent kidney loss and septicaemia. Ureteric catheterisation or percutaneous nephrostomy are the first steps (Dairiki-Shortliffe and Stamey, 1986). If successful, relief of symptoms occurs in 24 h; thereafter an aetiological factor can be sought.

In our opinion nephrectomy is mandatory, especially when the source of obstruction is not obvious, because of the possibility of cancer. If our 2 patients had been managed with open or percutaneous drainage alone, there would have been a significant delay in the diagnosis of cancer.

Rives *et al.* (1980), in a series of 12 patients who had renal abscesses, treated 6 with incision and drainage and 3 with nephrectomy. They found a greater incidence of wound infection in those who underwent open drainage rather than nephrectomy. The increasing role of interventional radiology has meant that percutaneous drainage has many supporters (Goldman *et al.*, 1977; Wright, 1977; Caltamone and Frank, 1980; Costello *et al.*, 1983). By contrast, Fernandez *et al.* (1985), in a series of 12 patients, treated 4 with percutaneous drainage but finally performed a secondary nephrectomy in 2 of them because of sepsis, while 2 who underwent nephrectomy and 4 with open drainage had an uneventful convalescence. They believed that renal exploration and open drainage should be the initial form of surgical treatment.

We believe that where the aetiology is unclear and the patient fails to respond to antibiotics, nephrectomy should be performed.

The role of kidney tumours as factors predisposing to pyonephrosis and renal abscess has not previously been stressed. This series has shown that

2 of 17 patients with pyonephrosis and 2 of 8 with renal abscesses had tumours of the kidney. In addition, 3 of 34 patients with renal carcinoma and 1 of 9 with transitional cell carcinoma of the renal pelvis presented clinically with serious infections of the kidney. The surgeon must keep in mind this possibility and be aggressive when managing pyonephrosis and renal abscess of unknown aetiology.

Acknowledgement

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Renal Hydatid Disease

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Summary—Hydatid disease is caused by the larval form of *Taenia echinococcus* (*Echinococcus granulosus*) in humans, the most common sites being the liver and the lungs. Involvement of the kidneys is uncommon and can be asymptomatic for long periods. Renal hydatid disease has no pathognomonic signs except for hydatiduria. Because of the risk of fatal anaphylaxis, puncture of the cyst should be avoided, and partial or total nephrectomy is still the preferred treatment. We present 10 patients with renal hydatid disease treated in the Department of Urology, Ankara University.

Echinococcosis is an infestation caused in humans by the larval form of *Taenia echinococcus* (*Echinococcus granulosus*). The viscera affected most often are the liver and the lungs (Matos and Rommel, 1979; Hertz *et al.*, 1984). Renal involvement constitutes approximately only 3% of all cases. Renal hydatid disease is usually encountered between the third and fifth decades of life and is extremely rare in children (Aragona *et al.*, 1984).

Patients and Methods

Ten patients were hospitalised and treated for renal hydatid disease between 1977 and 1988. The group included 6 females and 4 males with an age range of 11 to 50 years (mean 27.5). None had liver or lung involvement. Clinical, laboratory and radiological investigations were carried out (Table 1) and the findings are listed in Table 2.

Four were farmers and the rest had various occupations. Seven had hydatid disease in the left kidney (Fig. 1) and a renal mass was palpated in 5. The Casoni skin test was positive in only 1 patient; 1 had eosinophilia, 3 had pyuria and 2 had haematuria.

The radiological findings listed in Table 3 enabled us to make the correct diagnosis.

Table 1 Diagnostic Procedures

Detailed history, physical examination
Urine analysis
Blood count and biochemical tests
Casoni and Weinberg tests
Chest radiography
Radio-isotope liver scan
Intravenous urography
Ultrasound investigation (5 patients)
Radio-isotope renal scan (2 patients)
Angiography (2 patients)
Computed tomography (2 patients)
Findings at operation and examination of pathological specimens

Results

Nine of the 10 patients were treated surgically and in 8 cases nephrectomy was performed. Marsupialisation had to be carried out on 1 of the 9, who had a solitary kidney, while the tenth patient refused all treatment.

In 1 patient a hydatid cyst ruptured into the retroperitoneal region and a perinephric abscess developed. Scolices were detected while draining the abscess during surgery and only then was the patient diagnosed as having renal hydatid disease.

There was no operative or post-operative mortality and all patients have remained well.

Table 2 Symptoms, Findings, Laboratory Results and Treatment

Patient	Sex	Age	Kidney affected	Findings and symptoms	Laboratory tests	Treatment
E.T.	F	38	Left	Left lumbar pain, fever, malaise	Negative	Nephrectomy
S.C.	F	29	Left	Left lumbar pain, palpable mass	Pyuria	Nephrectomy
S.G.	M	17	Left	Left lumbar pain	Pyuria, haematuria	Refused
Ş.K.	M	39	Left	Left lumbar pain	Hydatiduria, Casoni test (+)	Nephrectomy
U.C.	F	11	Right	Right lumbar pain, palpable mass	Eosinophilia	Nephrectomy
Z.E.	F	22	Left	Left lumbar pain, palpable mass	Negative	Nephrectomy
D.D.	F	50	Right	Right lumbar pain, palpable mass	Haematuria	Marsupialisation
i.K.	M	24	Left	Left lumbar pain, nausea, vomiting	Pyuria	Nephrectomy
E.T.	F	18	Right	Right lumbar pain, palpable mass, fever	Negative	Nephrectomy
L.S.	M	32	Left	Left lumbar pain	Haematuria	Nephrectomy

**Fig. 1** Intravenous urogram showing hydatid cyst in the left kidney.

Discussion

Humans are accidental intermediary hosts for echinococcal cysts. Of the 3 species of the *Echinococcus* genus, *Echinococcus granulosus* is the one which most commonly affects humans.

The echinococcal eggs excreted in the faeces of dogs are acquired by intermediary hosts, which can be sheep, cattle or humans. The ingested hydatid eggs hatch in the duodenum and the hydatid larvae penetrate the duodenal and intestinal walls into the venules and are carried by the bloodstream to other organs (Kilinc *et al.*, 1983; Hertz *et al.*, 1984; Buckley *et al.*, 1985; Cohen, 1986).

The primary sites of larval invasion are the liver and the lungs. Renal involvement occurs in 2 to 3% of all hydatid cases (Diamond *et al.*, 1976; Aragona *et al.*, 1984; Nogues *et al.*, 1984) and may be either a primary or a secondary manifestation of the disease (Aragona *et al.*, 1984).

The echinococcal larvae may reach the kidneys through the bloodstream, the lymphatics or by direct inoculation (Aragona *et al.*, 1984). Although the kidney is the commonest site in the genitourinary tract, the prostate, bladder and epididymis may also be involved (Buckley *et al.*, 1985).

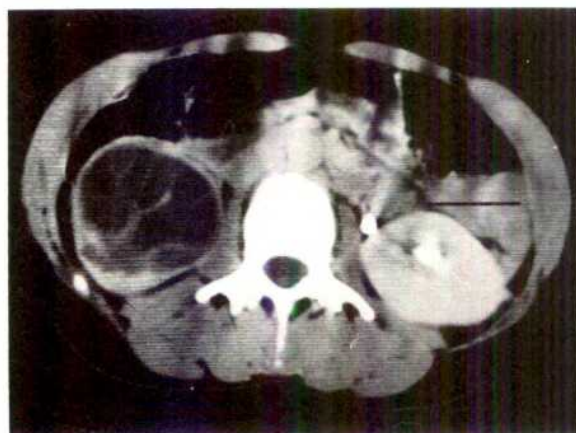
Echinococcal cysts of the kidney are usually single and located in the cortex (Fig. 2) (Martorana *et al.*, 1981; Hartman, 1985; Cohen *et al.*, 1986). The cysts vary in size from a few millimetres to a few centimetres.

After invasion of the intermediary host by the echinococcal larva, a tissue reaction rich in fibroblasts is initiated at the perinephrium of the cyst, and atrophy and pressure necrosis at the periphery of the cyst make the adventitial layer (Diamond *et al.*, 1976; Hartman, 1985). The cystic wall has no communication with the collecting system. Renal hydatid disease progresses slowly and remains asymptomatic for prolonged periods (Aragona *et al.*, 1984; Efstratopoulos *et al.*, 1984).

As a rule, the first symptoms are fever, a palpable mass and haematuria; if the cyst is secondarily infected, fever, rigors, pain and malaise may also be found (Kilinc *et al.*, 1983; Buckley *et al.*, 1985; Cohen *et al.*, 1986). The cyst sometimes ruptures into the collecting system and the patient experiences colic and passes debris resembling grape skins in the urine (hydatiduria). We observed this unusual finding in only 1 of our patients. If the cyst ruptures, the highly antigenic properties of the

Table 3 Radiological Findings

Examination	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Plain radiography										
Detection of mass	✓	✓		✓		✓			✓	✓
Calcification			✓				✓			
Intravenous urography										
Loss of function			✓	✓						
Caliceal distortion		✓			✓	✓	✓			✓
Caliectasia and hydronephrosis	✓				✓				✓	✓
Angiography										
Avascular mass		✓				✓				
Radio-isotope scanning										
Hypoactive region			✓						✓	
Ultrasound										
Calcified cystic wall								✓		
Mixed echogenic pattern								✓		✓
Computed tomography										
Calcified cystic wall				✓						
Multivesicular cystic structures				✓						✓

**Fig. 2** Computed tomography showing lobulated, cystic appearance of hydatid disease in the right kidney.

clear-fluid in the cyst cause urticaria and even an anaphylactoid reaction (Cohen, 1986).

There is no laboratory finding pathognomonic of hydatid disease except for hydatiduria. The Casoni skin test produces positive results in about 50% of patients, while the Weinberg test yields about 40% positive results. In only 1 of our patients was the Casoni skin test positive. Eosinophilia is detected in 20 to 50% of patients (Buckley *et al.*, 1985; Cohen, 1986).

In the radiological investigations the detection of a thick, calcified cystic wall suggests hydatid cyst (Aragona *et al.*, 1984; Cohen, 1986) because only 1

to 2% of simple renal cysts show calcification (Hertz *et al.*, 1984).

If the cyst ruptures into the collecting system, daughter cysts may be detected by injecting radio-contrast solution (Hartman, 1985; Cohen, 1986). Ultrasound and computed tomography usually reveal a multiloculated cystic formation containing small, daughter cysts. Renal radio-isotope scanning and angiography may prove helpful (Kilinc *et al.*, 1983; Hertz *et al.*, 1984; Hartman, 1985; Cohen *et al.*, 1986).

Management

Although aspiration of hydatid cysts has been reported, this procedure is not recommended because of the risk of dissemination and allergic reactions. Marsupialisation is also not recommended unless the patient has a solitary kidney, when the cyst can be first aspirated and then filled with a scolecidal agent such as 30% sodium chloride, 2% formalin, 1% iodine or 0.5% silver nitrate solutions (Buckley *et al.*, 1985; Cohen *et al.*, 1986).

There are reports that antihelminthic agents (mebendazole or albendazole) reduce the size of the cyst in some cases; however, these agents do not always give satisfactory results and they do have side effects (Kilinc *et al.*, 1983; Nabizadeh *et al.*, 1983; Morris *et al.*, 1985).

Surgery is the primary method of treatment and, according to the degree and extent of the formation of the renal hydatid cyst, a partial or total

nephrectomy is performed (Hertz *et al.*, 1984; Buckley *et al.*, 1985; Cohen, 1986).

In a study of a renal hydatid cyst with central pole localisation (Nogues *et al.*, 1984), bench surgery was carried out.

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Comparison of Clinical and Pathological Characteristics in Incidentally Detected and Suspected Renal Carcinoma

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Summary—In a study of the clinical and pathological characteristics of incidentally detected and suspected renal carcinoma, we reviewed the manner of presentation, serum immunosuppressive acidic protein (IAP), tumour stage and size in 112 consecutive patients with renal carcinoma who were diagnosed clinically and surgically between 1980 and 1989. The results showed an increase in the proportion of incidentally diagnosed cases. The routine use of radiological imaging, especially ultrasound and computed tomography (CT), has led to tumours being diagnosed earlier than when IAP is used as a tumour marker in patients with incidentally detected renal carcinoma. Tumours were lower stage and smaller in patients with incidentally detected renal carcinoma than in patients in whom the diagnosis was suspected.

Renal carcinomas are usually recognised as slow-growing tumours and most are detected following investigation of the various clinical signs. Recently, however, the widespread use of ultrasound and CT has increased the incidental detection of renal carcinoma (Konnak and Grossman, 1985; Ueda and Mihara 1987; Smith *et al.*, 1989), but there are few detailed reports comparing the clinical and pathological characteristics of incidentally detected and suspected renal carcinomas. The present study was carried out retrospectively to assess this situation.

Patients and Methods

We reviewed the medical records and radiological imaging studies of 112 patients with renal carcinoma who were diagnosed clinically and surgically between 1980 and 1989. Patients were divided into 2 categories: those hospitalised from 1980 to 1984 and those hospitalised from 1985 to 1989. All were

grouped according to whether the renal tumour was an incidental finding on ultrasound, CT, intravenous urography (IVU) or angiography, including investigations for medical examination and for the evaluation or diagnosis of various diseases (group A), or whether the renal tumour was suspected, including investigations for haematuria, flank pain, abdominal or flank mass, weight loss, suspected metastatic disease or fever (group B).

IAP values were evaluated pre-operatively as tumour markers in 28 patients in group A and 22 in group B; all had low stage lesions (stages I and II). IAP values were assayed by the single radial immunodiffusion method. The normal value was 500 µg/ml according to our previous data (Ueda, 1986).

The stage of the tumour was classified pathologically in 91 patients and clinically in 21 according to the classification of Robson (1969). The diameter of the lesions was measured on gross pathological specimens in 91 patients treated by nephrectomy and categorised as ≤2.5 cm, 2.6 to 5 cm, 5.1 to 10 cm and >10.1 cm. Statistical analysis was performed using Student's *t* test.

Results

In the 1980 to 1984 series, 11 patients (33.3%) were in group A and 22 (66.7%) in Group B. In the 1985 to 1989 series, 34 patients (43%) were in group A and 45 (57%) in group B. Their mean age was 61 years (range 27–80) in group A and 58 years (range 24–81) in group B. There were 27 men and 18 women in group A, and 44 men and 23 women in group B.

The diagnosis was first made by ultrasound in 31 patients (68.9%), by CT in 6 (13.3%), IVU in 6 (13.3%) and angiography in 2 (4.5%). Ultrasound was performed as part of their medical examination in 9 patients and for the diagnostic study of various diseases in 22. CT led to the diagnosis in 6 patients with other diseases. Five underwent IVU for the diagnosis of urological or gynaecological diseases, and 1 during follow-up of ureteric calculi in the 1980 to 1984 series. Angiography was performed for the pre-operative evaluation of heart disease and aortic aneurysm in 2 patients.

The mean value of IAP was 410.2 ± 34.9 $\mu\text{g/ml}$ in group A and 642.0 ± 217.4 $\mu\text{g/ml}$ in group B. There was a significant difference between the groups ($P < 0.01$). IAP was elevated pre-operatively to more than 500 $\mu\text{g/ml}$ in 6 patients (21.4%) in group A and 16 (72.7%) in group B with low stage lesions (Table 1). In 2 Group B patients the IAP level exceeded 1000 $\mu\text{g/ml}$.

Table 2 shows the clinical and pathological stage in 112 patients; 21 were not treated surgically and clinical staging was done in 3 patients (1 stage II and 2 stage III) in group A and 18 (1 stage II, 1 stage III and 16 stage IV) in group B.

The tumours ranged in size from 1 to 9.5 cm (mean 4.3 ± 2.1) in group A patients and from 2 to 20 cm (mean 7.1 ± 3.4) in group B; this difference was statistically significant ($P < 0.01$) (Table 3).

Discussion

Data obtained before 1980 revealed renal carcinoma as either an incidental finding or as a silent tumour in 5 to 28% of all cases (Ochsner *et al.*, 1973; Boxer *et al.*, 1979; Warren *et al.*, 1980). On the other hand, Konnak and Grossman (1985) reported that no less than 48% of 46 patients were incidentally diagnosed in their 1978 to 1984 series. In the present study, 43% were incidentally detected between 1985 and 1989 and 33.3% between 1980 and 1984. Our data reveal an increase in the proportion of such cases.

In recent years, various radiological imaging

Table 1 Pre-operative levels of IAP in Patients with Low Stage Lesions

Group	IAP ($\mu\text{g/ml}$)	
	≤ 500	> 500
A(28)	22 (78.6%)	6 (21.4%)
B(22)	6 (27.3%)	16 (72.7%)

Table 2 Clinical and Pathological Stage

Group	Stage					
	I	II	III			IV
			A	B	C	
A(45)	35 (77.8%)	6 (13.3%)	1 (8.9%)	2	1	0 (0%)
B(67)	24 (35.8%)	11 (16.4%)	3 (10.5%)	4	0	25 (37.3%)

Table 3 Tumour Size in Patients treated by Nephrectomy

Group	Tumour size (cm)			
	≤ 2.5	2.6–5.0	5.1–10.0	> 10.0
A(42)	9 (21.4%)	22 (52.4%)	11 (26.2%)	0 (0%)
B(49)	2 (4.1%)	15 (30.6%)	26 (53.1%)	6 (12.2%)

techniques have become widely used for the diagnosis of renal masses (Levine *et al.*, 1989) and ultrasound in particular has been used as a simple and non-invasive modality for abdominal examination (Gatenby, 1983; Takei *et al.*, 1987). Of 45 patients with renal carcinoma detected incidentally, 69% were first discovered by ultrasound; in some, the renal tumour was only 1 cm in diameter. Fewer tumours were detected by CT than by ultrasound, despite the high cost of CT examination. Nevertheless CT remains an important method for the incidental detection of renal masses (Komatz *et al.*, 1985; Levine *et al.*, 1989). With the increasing use of both ultrasound and CT, the number of renal carcinomas detected incidentally should continue to increase. IVU remains the radiological test used initially for the investigation of urinary tract disorders, but although renal masses were detected

incidentally by IVU in 6 patients (13.3%) all of them were discovered before 1985. In our previous study, IVU showed normal findings in 23.6% of 55 patients with renal carcinoma (Ueda *et al.*, 1989). Thus the value of IVU for the initial detection of renal masses is limited.

In 1986 we reported that IAP was a useful marker for renal carcinoma (Ueda, 1986). In order to study its usefulness in screening, IAP values were measured pre-operatively in patients with low stage lesions. The positive rate was 72.7% in suspected renal carcinomas but only 21.4% in those detected incidentally. Thus it seems that the measurement of IAP is limited to the detection of low stage lesions without clinical signs. However, IAP levels were significantly higher in patients with suspected renal carcinoma than in those with incidentally detected tumours and this shows that IAP can be used as a tumour marker for suspected renal carcinoma.

Tumour stage is an important prognostic factor in renal carcinoma. In our previous study, it was reported that low stage lesions were commoner in incidentally detected renal carcinomas than in suspected ones (Ueda and Mihara, 1987). Of 45 patients with incidentally detected tumours, 91% were low stage lesions. On the other hand, 47.8% were high stage lesions in 67 patients with suspected renal carcinoma and this result supports our previous data. Tumour size is also an important prognostic factor in renal carcinoma. It has been reported that there is a significant difference in survival between patients with tumours < 5 cm and those whose tumours exceed 10 cm (Nurmi, 1984; Medeiros *et al.*, 1988). The size of incidentally detected renal carcinomas is less than that of suspected ones (Ohnishi *et al.*, 1990). Our data have also shown a significant difference in mean tumour size between incidentally detected and suspected renal carcinomas. Moreover, tumours < 5 cm were found in 73.8% of incidentally detected renal carcinomas compared with 34.7% of suspected ones. These results will possibly mean longer survival in patients with incidentally detected renal carcinoma than in patients where the diagnosis was merely suspected.

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Characteristics of Mast Cells in Normal Bladder, Bacterial Cystitis and Interstitial Cystitis

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Summary—An analysis was made of the numbers and characteristics of mast cells in lateral bladder wall biopsies from 22 patients with interstitial cystitis, 6 with bacterial cystitis and 8 normal controls, using toluidine blue stains and computerised video image analysis techniques. A significantly greater number of mast cells were found within the detrusor muscle in interstitial cystitis than in bacterial cystitis or normal controls. Within the urothelium and submucosa, mast cell numbers were significantly greater than in normal controls in both interstitial and bacterial cystitis. In interstitial cystitis mast cells were significantly larger within the detrusor than in the urothelium/submucosa and they appeared to degranulate predominantly within the superficial layers. Differential staining techniques, using long and short toluidine blue stains, failed to reveal statistically significant evidence of mast cell heterogeneity within the bladder wall in interstitial cystitis.

Interstitial cystitis (IC) is a chronic idiopathic condition that predominantly affects middle-aged females. The diagnosis is made from the clinical history and cystoscopic findings (Gillenwater and Wein, 1988). The presence of a chronic inflammatory cell infiltrate, particularly within the submucosa, is a characteristic feature that may support the diagnosis (Lynes *et al.*, 1990). In severe cases the urothelium is denuded and this leads to the formation of Hunner's ulcer (Hunner, 1915). The presence of mast cells (MC) within the bladder wall in IC was first recognised in 1958 (Simmons and Bunce, 1958) but treatment with the antihistamine drug pyribenzamine did not bring about lasting symptomatic benefit (Simmons, 1961), suggesting that IC is not a purely allergic condition. A more recent study examined the location of MC throughout the bladder wall in IC and showed that IC was associated with a significant increase in MC numbers within the detrusor muscle (Larsen *et al.*, 1982). In a further report from the same centre,

MC counts in IC were compared with those in other forms of chronic cystitis and it was concluded that MC counts within the detrusor $> 20/\text{mm}^2$ had a diagnostic specificity of 88% and a sensitivity of 95% for IC (Kastrup *et al.*, 1983).

MC heterogeneity was first described by Enerbäck (1966) and MC subtypes were identified by their staining characteristics. Differential staining was shown to depend upon ionic linkages between glycosaminoglycans (GAG) molecules within MC granules (Enerbäck, 1966; Wingren and Enerbäck, 1983). The staining of MC has been shown to depend upon the fixation technique as well as the stain (Strobel *et al.*, 1981). Aldehyde fixatives block dye-binding sites within mucosal MC granules, but this block can be overcome by using very long staining times (Wingren and Enerbäck, 1983). A differential staining technique, using 4% buffered formaldehyde fixation followed by toluidine blue stain (30 min for short toluidine blue or STB; 5 days for long toluidine blue or LTB), was used to study MC in IC. The STB was thought to show connective tissue MC only whilst LTB showed both mucosal and connective tissue MC. It was concluded that mucosal MC were predominantly present within the submucosa and migrated through the urothel-

ium into the bladder lumen, while connective tissue MC were mostly found within the detrusor (Aldenborg *et al.*, 1986).

The aim of this study was to count the numbers of MC present and to determine the site of degranulation and the characteristics of MC in patients with IC, and to compare them with normal controls and patients with bacterial cystitis.

Patients and Methods

Biopsies were taken from the lateral wall of the bladder in 22 patients with IC diagnosed according to established criteria, 6 patients with chronic bacterial cystitis (BC) and 8 normal controls. Two biopsies were taken from each patient and immediately fixed in 4% formaldehyde in 0.5M buffer (BF) for 24 h and then embedded in paraffin wax and 5 µm sections cut prior to storage. The slides were then deparaffinated in xylene, passed through absolute alcohol and alcohol dilutions, washed with water and stained simultaneously for 30 min (STB) or 7 days (LTB) in 0.5% toluidine blue (CI 52040, Merck) in 0.5M hydrochloric acid (pH 0.5). This technique stains MC granules with a weak background stain (Fig. 1). The slides were examined using an Olympus BH-2 microscope at ×25 magnification. In order to quantify the number of MC, their area in pixels and their integrated optical

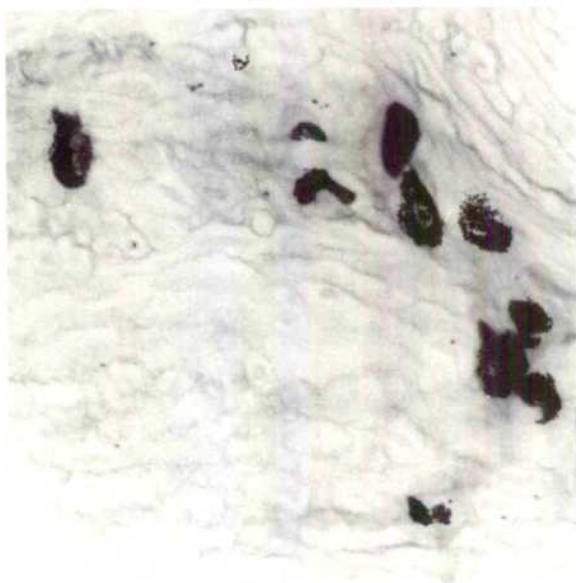


Fig. 1 Lateral bladder wall biopsy fixed with buffered formalin and stained with toluidine blue for 7 days. Mast cell granules are stained darkly within the detrusor muscle.

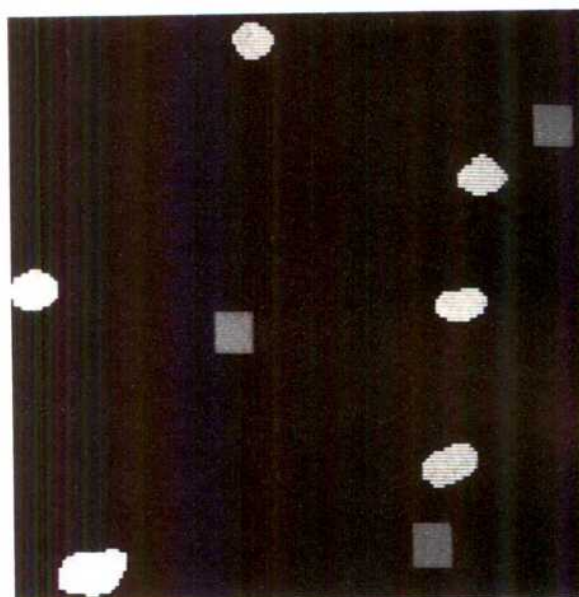


Fig. 2 Computerised video image analysis scan of MC from bladder wall biopsy. Artifacts have been erased (squares).

density (IOD), the biopsies were screened using a computerised video image analysis (CVIA) system (Jarvis, 1986) obtained from Flinders University, Adelaide, Australia, and incorporating a Zenith Z100 computer with a 30 Mbyte hard disk (Fig. 2). The urothelium/submucosa and detrusor muscle areas were analysed separately. Any artifacts present on the slides were erased. A total of 10 fields in each area was studied in each biopsy.

The results were analysed using the Mann Whitney U-test and Wilcoxon test since they were not of Gaussian distribution.

Results

In all patients there was even, clear staining of MC with pale background staining enabling morphometric analysis to be performed by CVIA without erasure of many artifacts. Since the nuclei were of uniform size and there was no evidence of MC division on any of the slides, the MC area and IOD were judged to be a reflection of the individual MC granule burden.

Long toluidine blue staining

MC counts after BF fixation and LTB staining are shown in Table 1. The urothelium/submucosa MC counts in IC were significantly greater than in normal controls ($P=0.0005$). Urothelium/submucosa MC counts in BC were also significantly

Table 1 Mast Cell Analysis After Buffered Formalin Fixation and Long Toluidine Blue Staining

	Numbers		Area (pixels)		IOD	
	<i>Urothelium/ submucosa</i> Median (range)	<i>Detrusor</i> Median (range)	<i>Urothelium/ submucosa</i> Median (range)	<i>Detrusor</i> Median (range)	<i>Urothelium/ submucosa</i> Median (range)	<i>Detrusor</i> Median (range)
Interstitial cystitis	146 (50–284)	170 (83–380)	18.7 (10.1–24)	19.8 (13–33.7)	5.0 (2–6.5)	5.8 (2.5–9.2)
Bacterial cystitis	97 (69–222)	45 (34–90)	16.7 (15–22.1)	18.0 (11.2–21)	4.4 (4–5.4)	4.6 (3.0–6.1)
Normal controls	51 (15–83)	46 (10–66)	14.2 (9.7–16)	17.0 (10–17.2)	3.2 (2–4)	3.2 (2.3–4.5)

Numbers per 10 high power fields ($\equiv 1.665 \text{ mm}^2$).

Table 2 Mast Cell Analysis After Buffered Formalin Fixation and Short Toluidine Blue Staining

	Numbers		Area (pixels)		IOD	
	<i>Urothelium/ submucosa</i> Median (range)	<i>Detrusor</i> Median (range)	<i>Urothelium/ submucosa</i> Median (range)	<i>Detrusor</i> Median (range)	<i>Urothelium/ submucosa</i> Median (range)	<i>Detrusor</i> Median (range)
Interstitial cystitis	136 (60–352)	184 (60–512)	11.0 (5.7–17)	18.7 (11–32)	6.7 (2.1–10.3)	12.2 (6–27.6)
Bacterial cystitis	128 (36–204)	40 (16–100)	12.1 (9.9–17)	13.9 (10–20.2)	7.6 (5.9–10.6)	8.0 (4.6–12.8)
Normal controls	52 (32–132)	16 (8–96)	10.7 (7.4–15)	17.9 (10.4–26)	5.8 (3.4–8.7)	7.5 (3.3–15.3)

Numbers per 10 high power fields ($\equiv 1.665 \text{ mm}^2$).

greater than in normal controls ($P=0.0067$) but were not significantly different from MC counts in IC ($P=0.33$). The detrusor MC count in IC was significantly greater than in BC ($P=0.0005$) and normal controls ($P=0.0081$). There was no significant difference between detrusor MC counts in normal controls and in BC ($P=0.25$).

The size of MC in pixels within the urothelium/submucosa in the study cases is shown in Table 1. The size of MC within the urothelium/submucosa in IC was significantly greater than in normal controls ($P=0.0009$), but the same did not apply in BC ($P=0.26$). The size of MC within the urothelium/submucosa was greater than normal in BC ($P=0.0055$). The size of MC within the detrusor was not significantly greater in IC than in BC ($P=0.13$) or normal controls ($P=0.11$).

The IOD of MC is shown in Table 1. The MC in the urothelium/submucosa layer were of significantly greater IOD in IC than in normal controls ($P=0.0032$). However, there was no difference between MC IOD in IC and BC ($P=0.35$). The MC within the urothelium/submucosa in BC were also of significantly greater IOD than in normal controls ($P=0.0037$). Within the detrusor there were no significant differences between MC IOD in the individual groups.

A comparison between MC numbers and characteristics within the urothelium/submucosa and

detrusor layers was performed in order to assess the site of activity. In normal controls there was no difference between the number of MC within the 2 layers, their size or their IOD. In BC, MC were significantly more abundant within the urothelium/submucosa than in the detrusor layer ($P=0.036$). However, in BC there was no significant difference between the size or IOD of MC in the 2 layers. In IC the number of MC within the urothelium/submucosa and detrusor was not significantly different but the MC within the detrusor layer appeared to be larger than those within the urothelium/submucosa; this difference approached statistical significance ($P=0.061$), suggesting that in interstitial cystitis the MC might degranulate within the more superficial layer. Furthermore, in interstitial cystitis the MC appeared to be of greater IOD within the detrusor than in the urothelium/submucosa and again the difference approached statistical significance ($P=0.061$).

Short toluidine blue staining

The same analysis was performed after BF fixation and STB staining and the results are shown in Table 2. With this staining technique a significantly greater number of MC were found within the urothelium/submucosa in both IC ($P=0.0003$) and BC ($P=0.031$) than in normal controls. Detrusor

MC counts were significantly greater in IC than in BC ($P=0.0026$) and normal controls ($P=0.0001$). The areas of MC within the urothelium/submucosa were not significantly different between the various groups. However, detrusor MC were significantly larger in IC than BC ($P=0.043$). The IOD of MC within the urothelium/submucosa was not significantly different between the groups. Detrusor MC were, however, of greater IOD in IC than in normal controls ($P=0.04$).

A comparison between the characteristics of MC within the urothelium/submucosa and detrusor revealed some differences. In normal controls there was no significant difference between IC counts within the urothelium/submucosa and detrusor but the detrusor MC were significantly larger ($P=0.014$) and of greater IOD ($P=0.03$) within the detrusor layer than in the urothelium/submucosa. In BC there was no such difference in MC numbers, size and IOD between the urothelium/submucosa and detrusor. However, this may have been partly due to the fact that 2 of the BC STB-stained biopsies could not be adequately evaluated because of missing portions of tissue. As with LTB staining in IC, the number of MC was not significantly different between the urothelium/submucosa and detrusor. However, in IC the intramuscular MC were significantly larger ($P=0.0001$) and of greater IOD ($P=0.0001$) than the MC within the urothelium/submucosa.

Comparison of staining techniques

MC counts within the urothelium/submucosa after BF fixation/STB staining were lower than with BF fixation/LTB staining but the difference was not statistically significant ($P=0.55$). The same applied to intramuscular MC ($P=0.24$). A comparison of the area of MC after STB and LTB staining in the IC group revealed that within the urothelium/submucosa, LTB-stained MC were significantly larger (by a mean of 60.1%) than STB-stained MC ($P=0.001$); within the detrusor, LTB-stained MC were a mean of 13% larger than STB-stained MC; this difference was not quite statistically significant ($P=0.061$). Although granules within urothelial/submucosal MC in IC appear to stain less readily with STB than those within the detrusor, there was no significant evidence to support the concept of clear-cut MC heterogeneity within the bladder wall in IC, at least according to previously reported MC staining characteristics (Wingren and Enerbäck, 1983; Aldenborg *et al.*, 1986).

Discussion

This study has shown a significant increase in the number of MC within the detrusor muscle in IC when compared with normal controls and BC, confirming the findings of previous reports (Larsen *et al.*, 1982; Kastrup *et al.*, 1983; Aldenborg *et al.*, 1986; Lynes *et al.*, 1987). The results have also shown a significantly greater MC density within the urothelium/submucosa in IC than in normal controls, a finding that conflicts with previous studies in which no such difference was apparent (Larsen *et al.*, 1982; Kastrup *et al.*, 1983; Lynes *et al.*, 1987). However, each of these studies used different staining techniques. A high urothelial/submucosal MC count in IC has been shown after toluidine blue (Aldenborg *et al.*, 1986) and saffron/alcan blue (Feltis *et al.*, 1987) stains and it is likely that failure to demonstrate MC within the superficial layers in the other studies relates to the inefficiency of the staining techniques in demonstrating small MC within the urothelium/submucosa. Detrusor MC counts in IC after BF fixation and LTB staining ranged from 30 to 228/mm² in this study and 13 to 103/mm² using naphthol-ASD-chloroacetate stain (Kastrup *et al.*, 1983). The mean detrusor MC count in this study was 99.5/mm² as compared with 62/mm² using naphthol-ASD-chloroacetate (Larsen *et al.*, 1982), 18.5/mm² using haematoxylin phloxine saffron and alcian blue (Feltis *et al.*, 1987) and 57.6/mm² using pinosulium erythrosuxinate stain (Lynes *et al.*, 1987). This comparison reveals the huge variability in the efficiency of fixation and staining techniques in demonstrating MC and confirms that LTB appears to be the most comprehensive and effective stain for MC (Wingren and Enerbäck, 1983; Aldenborg *et al.*, 1986).

The presence of large numbers of MC within the bladder wall in IC suggests that they might have a role in the pathogenesis of the condition. However, an increase in MC numbers within the bladder wall is not restricted to IC since in BC there is also an increase, but this is restricted to the urothelium and submucosa. In the majority of cases, BC commences within the lumen of the bladder and spreads to involve the superficial layers without involving the detrusor muscle. This suggests that, at least in BC, the increase in bladder wall MC numbers is a feature of the chronic inflammatory reaction. The presence of MC infiltrate within the urothelium and submucosa in BC has been reported by Cornish *et al.* (1986). Previous studies of MC in IC have either not included a BC control group (Aldenborg

et al., 1986; Lynes *et al.*, 1987), merged BC cases with other forms of chronic cystitis as a control group (Kastrup *et al.*, 1983) or included only 3 cases of BC, as in the study by Larsen *et al.* (1982). However, all of the studies in which forms of chronic cystitis other than IC have been included as control groups have, as in the present study, failed to show a significant difference between MC numbers within the urothelium/submucosa in IC and all other forms of cystitis. This suggests that at least as far as the urothelium/submucosa is concerned, the presence of MC in cystitis, whatever the aetiology, is part of the inflammatory cell infiltrate rather than a specific feature of IC.

The results presented here are not in accord with the only previous study of MC heterogeneity in the bladder in IC (Aldenborg, 1986). Although the amount of stain taken up by MC was greater after LTB than STB, particularly within the urothelium/submucosa, there was no significant difference between MC counts with the 2 staining techniques. These findings do not support the hypothesis that there is clear-cut evidence of MC heterogeneity in the bladder in normal controls, BC or IC.

The activity of MC within the bladder wall in IC has been examined in only 1 previous study (Lynes *et al.*, 1987). The proportion of MC that appeared to be degranulated was counted in histological sections and it was concluded that degranulation occurred uniformly throughout the bladder wall in IC. Examination of MC after LTB and STB staining in this study revealed a greater number of degranulated MC within the urothelium and submucosa than the detrusor. In order to quantify this finding objectively, morphometric MC analysis has been performed and this is the first study to analyse the characteristics of individual MC in the bladder by CVIA techniques. Since MC are such potent cells, the site of their action might give some indication of the pathogenesis of IC. In IC, MC are larger than in normal controls, suggesting that they are more actively manufacturing intracytoplasmic granules; they are also significantly smaller and less densely stained within the urothelium/submucosa, which appears to confirm the impression that degranulation occurs predominantly within the superficial layers and that the stimulus for the pathogenesis of IC is within or near to the urothelium. No such differences were apparent in the control groups. The precise stimulus for MC degranulation is not clear, but CD4+ and CD8+ T cells are known to infiltrate the urothelium/submucosa but not the detrusor in IC (MacDermott *et al.*, 1989; Christmas *et al.*, 1990b) and could play

a role in inducing MC degranulations. Furthermore, T cells are also known to induce MC growth and proliferation by release of interleukin-3 (Watson and Prestidge, 1983) and this may occur in IC. It has been suggested, largely because of their close anatomical proximity, that MC granule exocytosis may be stimulated by autonomic nerve fibres (Heine and Förster, 1975). Proliferation of autonomic nerve fibres is known to occur within the bladder wall in IC (Christmas *et al.*, 1990c) and it is tempting to speculate that the autonomic nervous system might in some way control MC function in IC, as postulated in the colon in ulcerative colitis (Stead *et al.*, 1989).

MC appear to play a role in the pathogenesis of IC. The increase in the number of these cells and their apparent degranulation within the urothelium/submucosa, where the disease activity is greatest in IC, supports this suggestion. Aberrant urothelial HLA-DR expression has been shown in IC (Christmas *et al.*, 1990a) and this, in association with autologous antigen, can lead to activation of helper T cells and autoimmune attack against the urothelium. Degranulation of MC within the urothelium leading to the release of potent enzymes could contribute to the ultimate destruction of the urothelium in IC. However, it should be emphasised that the presence of MC in bladder biopsies cannot be used in isolation to diagnose IC.

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Sex Distribution of Adult Idiopathic Detrusor Instability in Relation to Childhood Bedwetting

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Summary—The urodynamic case records of 1000 consecutive men and women were reviewed to study the link between idiopathic detrusor instability (DI) and childhood nocturnal enuresis and to determine whether a sex difference in this relationship may exist.

Idiopathic DI was found in 10% of the men, 63% of whom had suffered from childhood bedwetting; 29% of the women had idiopathic instability, of whom 38% had been nocturnal enuretics. Thus the link between adult idiopathic DI and childhood bedwetting appeared to be stronger for men than for women.

The sex distribution of subjects is not always reported in urodynamic studies of bedwetters and adults with an unstable bladder. We suggest that this should become routine practice as it may help to shed light on the aetiology of idiopathic detrusor instability.

Childhood nocturnal enuresis is reported to be more common in school-aged boys than girls (Klackenberg, 1981; Verhulst *et al.*, 1985). However, bedwetting is not routinely investigated by cystometry, so that the incidence of underlying detrusor instability is uncertain. Two studies of bedwetting children showed that bladder instability was much more common in diurnal enuretics than in nocturnal enuretics, but the sex distribution was not fully described (Whiteside and Arnold, 1975; Mayo and Burns, 1990).

Previous studies on the aetiology of childhood enuresis have suggested that 2 varieties of the condition may exist. One may be a developmental disorder, more common in boys, which is not associated with excess emotional disturbance and consists mainly of night wetting. The other form, said to be more common in girls, is associated with behavioural problems and consists chiefly of day-wetting (Rutter *et al.*, 1973). However, others have drawn attention to the strong relationship between diurnal enuresis in schoolgirls and recurrent bacterial cystitis (Savage *et al.*, 1973; Hansson *et al.*, 1990).

The aetiology of idiopathic detrusor instability remains unknown. Studies which follow childhood enuretics into adulthood in order to observe detrusor physiology are fraught with difficulty, but would shed light on whether a sex difference may persist.

It has been our clinical impression that lifelong enuretics who eventually require surgical treatment are predominantly male (Gibbon *et al.*, 1973), whilst females often acquire instability despite a dry childhood. The purpose of the present study was to test this hypothesis by comparing the incidence of childhood enuresis in a group of adult men and women with urodynamically proven idiopathic detrusor instability.

Patients and Methods

The urodynamic case records of 500 consecutive adult females who had undergone urodynamic testing by the first and second authors over 15 months, and 500 adult males seen by the third author over 25 months, were reviewed. All had presented with lower urinary tract symptoms. The males (mean age 55 years, median 57, SD 17.4, range 17–92) tended to be older than the females (mean age 48 years, median 45, SD 12.6, range 18–

83). A detailed history was taken using a standardised proforma and troublesome childhood nocturnal enuresis persisting beyond the age of 6 years was recorded.

A midstream urine specimen was confirmed as negative for significant bacteriuria. Patients underwent either medium fill (100 ml/min) 4-channel videocystourethrography or cystometry, according to the provisional clinical diagnosis. Studies were performed in the supine position with standing provocation; voiding studies used the seated position for women and erect for men. Idiopathic DI was defined as uninhibited detrusor contractions > 15 cm H₂O during medium fill cystometry, in the absence of neuropathy or outflow tract obstruction.

The data were treated as follows. Firstly, all men and women with proven idiopathic DI were analysed in relation to their history of childhood nocturnal enuresis. The following patients were analysed separately: (1) males who had undergone prostatectomy or bladder neck incision; such men may have persistent instability despite relief of their obstruction (Fitzpatrick *et al.*, 1979) and so require urodynamic testing; (2) females who had undergone suprapubic bladder neck suspension and so had an 18% likelihood of developing DI (Cardozo *et al.*, 1979); (3) all patients over the age of 70, who may develop DI secondary to degeneration of the central nervous system (Williams and Pannill, 1982). Secondly, the converse relationship was examined: all patients with a history of childhood enuresis were analysed with respect to urodynamic diagnosis and sex. The possibility that older subjects might have poorer recall of childhood enuresis was also considered.

Methods, definitions and units conform to the standards recommended by the International Continence Society (Abrams *et al.*, 1988) except where specifically noted.

Results

The urodynamic diagnoses for the 1000 patients are shown in Table 1. The most common urological disorder in females was genuine stress incontinence (GSI), whilst in males it was bladder outflow obstruction with coexistent DI. No urodynamic abnormality could be found in 6% of women and 12% of men.

A total of 101 males were unstable and showed no urodynamic evidence of obstruction. Of these, 36 had undergone prostatectomy or outflow tract surgery, of whom 1 had a history of childhood

Table 1 Urodynamic Diagnoses

<i>Urodynamic diagnoses</i>	<i>Males (%)</i>	<i>Females (%)</i>
Obstructed, stable	87 (17.4)	13 (2.6)
Obstructed, unstable	128 (25.6)	12 (2.4)
Detrusor hyper-reflexia	81 (16.2)	8 (1.6)
Others	12 (2.4)	28 (5.6)
Unobstructed, atonic	11 (2.2)	16 (3.2)
Unobstructed, hypersensitive	20 (4.0)	27 (5.4)
Unobstructed, stable (NAD)	59 (11.8)	32 (6.4)
Genuine stress incontinence	1 (0.2)	190 (38.0)
GSI + unobstructed unstable	0 (0)	56 (11.2)
Unobstructed, unstable	101 (20.2)	118 (23.6)
Total	500 (100)	500 (100)

bedwetting; 14 were aged > 70 years, none of whom had been enuretics. Thus 51 men (10%) were found to have purely idiopathic DI. Of the 174 females with instability alone or combined GSI, 13 had undergone bladder neck suspension procedures, including 2 who had been bedwetters; 14 were over the age of 70, including 1 who had been enuretic. Thus 147 females (29.4%) were considered to have idiopathic DI.

Of the 198 patients with idiopathic instability, a history of childhood nocturnal enuresis was significantly more common in men (32/51, 63%) than in women (56/147, 38%) ($\chi^2 = 9.54$, $P < 0.01$).

Conversely, the 140 patients with a history of childhood nocturnal enuresis are shown in Table 2, in relation to their urodynamic diagnosis and age. Of the 50 males with a history of enuresis, 38 (76%) had unstable bladders. Of the 90 females with a history of enuresis, 55 (61%) were unstable ($\chi^2 = 5.38$, $P < 0.025$).

We also noted that the likelihood of a previous bedwetter having a urodynamically stable bladder in adulthood appeared to vary according to sex. Of the 50 male enuretics, only 8 (16%) were found to have a stable bladder, whereas 34 of the 90 female enuretics (37%) were urodynamically stable ($\chi^2 = 6.26$, $P < 0.02$).

Age at the time of history-taking had little association with ability to remember childhood bedwetting: the 50 males who recalled enuresis tended to be younger (mean age 35.8 years, range 17–77) than the 90 females who remembered wetting their beds (mean age 44.3 years, range 18–83).

Discussion

The distribution of diagnoses in our patients is similar to that reported in an earlier British series

Table 2 Patients with Previous Bedwetting History in Relation to Urodynamic Diagnosis and Age

<i>Diagnosis</i>	<i>Males</i>	<i>Mean age (years)</i>	<i>Females</i>	<i>Mean age (years)</i>
Obstructed, stable	3	52	2	38
Obstructed, unstable	6	44	2	48
Detrusor hyper-reflexia	4	34	—	—
Others	—	—	2	56
Unobstructed, atonic	—	—	—	—
Unobstructed, hypersensitive	4	40	4	37
Unobstructed, stable	1	29	4	44
Genuine stress incontinence	—	—	24	43
GSI+unstable	—	—	14	44
Unobstructed, unstable	32	33	39	44
Total	50	35.8	90	44.3

(Abrams *et al.*, 1983). Our sample is therefore likely to be representative of urodynamic patients in general. It must be noted that no abnormality was detected in 6% of women and 12% of men, and approximately 5% of both sexes had sensory urgency. Ambulatory urodynamics (Webb *et al.*, 1989) or diuresis cystometry (van Venrooij *et al.*, 1990) have a greater diagnostic yield for detrusor instability in patients with the "urge syndrome". Had these more sensitive tests been performed, the relationship between bedwetting and adult instability in men and women might have been altered.

In view of the known difference in the incidence of instability amongst daywetters and nightwetters, it is unfortunate that our standardised case sheet does not include details of childhood daywetting. Other published proformas also lack such detail (Stanton, 1984). However, we became aware anecdotally that many women recalled their mother sending a note to the schoolteacher allowing free access to the toilet during class in order to avoid urine leakage, but this was not commonly recalled by men. A more detailed study of these factors is now in progress.

Our study gives some support to the hypothesis that the link between childhood bedwetting and adult instability is stronger for men than for women. Two-thirds of the males with idiopathic instability recalled troublesome childhood enuresis, in sharp contrast to the one-third of unstable women who had been bedwetters. Thus two-thirds of the unstable women appeared to have acquired detrusor instability despite a dry childhood.

The converse analysis revealed a less strong (although significant) association; of all patients with a bedwetting history, 76% of men and 61% of women were found to be unstable. However, it was interesting to note that previous male bedwetters

were considerably less likely to have a urodynamically stable bladder (16%) than females who had wet the bed in childhood (37%).

As research into the cause of idiopathic detrusor instability continues, the possibility of a male predilection for lifelong bladder overactivity should be borne in mind. In particular, the sex distribution of all children and adults who are investigated for bedwetting, daywetting and urge incontinence should be specifically reported in relation to their urodynamic diagnosis.

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Authors' Addendum

Professor E. P. Arnold has kindly reviewed his original data (Whiteside and Arnold, 1975) and carried out the following analysis of sex distribution by urodynamic diagnosis.

Of the 42 adults who presented with a history of previous enuresis beyond the age of 7 years, there were 16 men, of whom 14 (87%) were found to have unstable bladders. There were 26 women with such a history, of whom 17 (65%) were found to be unstable.

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Subtrigonal Phenol Injection. How Safe and Effective is it?

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Summary—A series of 24 patients underwent 27 transtrigonal phenol injections for the treatment of bladder instability. Only 2 of 18 patients with detrusor instability and 2 of 6 with detrusor hyper-reflexia continued to derive benefit from the procedure 6 months after it was carried out. Serious complications attributable to phenol were seen in 2 patients in this series and in a further 4 patients referred for complications resulting from this therapy in other centres. These results and a review of the literature lead us to suggest that transvesical phenol injection should not be used except in the hyper-reflexic bladder when no alternative treatment is possible. Particular care should be exercised in patients who have undergone extensive prior surgery or radiotherapy.

The symptoms of bladder overactivity resulting from detrusor instability or hyper-reflexia are distressing for the patient and their satisfactory management is often problematic for the clinician. Bladder training supplemented where necessary by the use of anticholinergic agents and the occasional use of DDAVP form the mainstay of treatment (Frewen, 1978; Moisey *et al.*, 1980). Once these measures have failed it has been suggested that prior to embarking on major surgery, transtrigonal phenol injection therapy may be useful (Ewing *et al.*, 1982). Although initial series (Ewing *et al.*, 1982; Blackford *et al.*, 1984; Cameron-Strange and Millard, 1988) reported favourable results, later reports have suggested it to be more limited both in terms of success and duration of action (Nordling *et al.*, 1986; Wall and Stanton, 1989; Rosenbaum *et al.*, 1990). We report our experience with this technique in 24 patients and review the complications resulting from this therapy in a further 4 patients referred to our unit. Both of these aspects are discussed in the context of the current world literature.

Patients and Methods

A total of 24 patients underwent 27 transvesical subtrigonal phenol injections for symptoms of

bladder instability. The group comprised 18 patients (15 women) of mean age 52.3 ± 4.3 years with detrusor instability (DI) and 6 patients (5 women) of mean age 50.8 ± 7.2 years with detrusor hyper-reflexia (DHR). The DI group were idiopathic in aetiology. The DHR group included 2 patients with multiple sclerosis (MS), 2 post cerebrovascular accidents (CVA) and 1 each motor neurone disease (MND) and dementia. The mean follow-up after phenol injection was 14.7 ± 2.7 months for DI patients and 11.7 ± 4.0 months for the DHR group.

All patients underwent videocystometry and all had been treated with conventional therapy, including bladder retraining and pharmacotherapy. Transtrigonal injection of a 6% aqueous solution of phenol was carried out under general anaesthesia following the guidelines laid down by Ewing *et al.* (1982). Patients were allowed home the following day and were reviewed in out-patient clinics for the first 6 months and thereafter as necessary.

Results

Detrusor Instability Group. Ten of the 18 women reported an improvement at 1 month. This figure fell to 7/18 at 3 months and 2/18 at 6 months. Three patients had 2 injections of phenol; 2 of them derived no benefit at all from either injection and 1 had only a transient response (4 months). Two

patients had urodynamic studies which reverted to stability after the injections but failed to show any subjective improvement at 3 months.

Detrusor Hyper-reflexia Group. Improvement was seen in 4 of the 6 patients at 3 months. Two (1 MS, 1 CVA) became wet again by the 6-month review but 2 patients (1 MND, 1 MS) with indwelling catheters have ceased leaking around their catheters and this improvement was maintained at the 12-month review. A 69-year-old with dementia failed to show any improvement and a 32-year-old with a previous CVA developed a vesicovaginal fistula 2 months after injection. This was repaired via an abdominoperineal approach and she subsequently underwent an enterocystoplasty with good result.

Complications. There were 2 significant complications in this series (cases 1 and 2), with a further 4 patients who had been treated at other centres being referred for the further management of complications (cases 3 to 6).

Case Reports

Case 1. A 63-year-old female with severe detrusor instability was improved after phenol injection therapy for 4 months. A second injection was followed 6 weeks later by a vesico-ureterovaginal fistula. She underwent a successful repair of this, which was associated with a marked vaginal fistula. This was repaired successfully but was associated with marked tissue fibrosis related to her phenol injection therapy. She was troubled by persistent urinary incontinence and on examination was found to have a rigid patulous urethra associated with marked periurethral fibrosis. A reduction sphincteroplasty restored full urinary continence.

Case 2. A 32-year-old female with detrusor hyper-reflexia underwent transtrigonal phenol injection therapy. She was not improved and 2 months later developed a vesicovaginal fistula. This was repaired using a combined abdominoperineal approach; at surgery dense fibrosis was evident in the perivesical tissues at the base of the bladder. A clam enterocystoplasty was then successfully carried out.

Case 3. A 70-year-old female was referred with recalcitrant detrusor instability and continuous urinary incontinence. She had previously undergone 2 vaginal and 2 abdominal surgical repairs which had proved unsuccessful and had then been treated with transtrigonal phenol therapy; 4 weeks after this she had become continuously incontinent of urine. On examination she was found to have a rigid "pipe-stem" urethra. At surgical exploration the base of the bladder and periurethral area were encased in dense fibrous tissue. A reconstructive procedure was not possible and urinary diversion was carried out.

Case 4. A 20-year-old female was referred with complications resulting from transtrigonal injection therapy. She had been treated with 2 injections spaced 8 months apart. An increase in functional bladder capacity resulted and her symptoms were improved. Eight months later she presented with bilateral loin pain and recurrent urinary incontinence and on investigation was found to have right vesicoureteric reflux, left ureteric stenosis and stress incontinence; these abnormalities were felt to be a result of her phenol injection therapy. At subsequent surgery, when bilateral ureteric reimplantation was carried out, she was found to have dense fibrosis at the base of the bladder and around the bladder neck and urethra. Following an additional bladder neck repositioning procedure and clam cystoplasty she was rendered symptom-free.

Case 5. A 71-year-old female was referred with urinary retention following transtrigonal phenol injection therapy. Pre-operative urodynamic assessment had demonstrated detrusor instability and repeated investigations post-operatively have shown detrusor hypocontractility. She is now on long-term intermittent self-catheterisation.

Case 6. A 48-year-old female with detrusor instability was referred with a vesicovaginal fistula which developed 4 weeks after phenol injection therapy. She had been treated with radiotherapy for carcinoma of the cervix several years previously. The fistula was successfully repaired via an abdominoperineal route and she remains free of detrusor instability 22 months later.

Discussion

Phenol is a potent neurolytic agent which in concentrations greater than 5% produces a non-reversible denaturing of protein (Nathan *et al.*, 1965) and when administered experimentally (in rats) directly to the paravesical plexus results in denervation of the detrusor muscle (Parkhouse *et al.*, 1987). The rationale behind the use of transtrigonal phenol injections is that the consequent damage to nerves in the paravesical pelvic plexus should result in a relative detrusor hypocontractility and hence the abolition of unwanted detrusor contractions.

A review of the literature on the use of transtrigonal phenol injections over the last 10 years reveals documentation of 318 patients undergoing 370 procedures. The largest groups were patients with DI and DHR; 56 of 153 DI patients (37.5%) were considered to have derived benefit and maintained improvement 3 months after treatment. The DHR group achieved a better success rate, with 61 of 107 patients (63.7%) improved at 3 months. The patients in the other 2 treatment categories (hyper-

Table 1 Published Series of Transvesical Phenol Injection

Author	Year	Patients/ injections	Detrusor instability	Detrusor hyper-reflexia	Post-operative hyperaesthesia
Ewing <i>et al.</i>	1982*	30	7	23 [20 MS]	
Ewing <i>et al.</i>	1983	24	24 (19)†		
Blackford <i>et al.</i>	1984	116	63 (25)	25 (21)	28 (16)
Nordling	1986	16/19		16 (3)	
Cameron-Strange and Millard	1988	40	29 (17)	11 (8)	
Wall and Stanton	1988	28/40	18 (4)	8 (3)	2 (1)
Rosenbaum <i>et al.</i>	1990	60/94	25 (3)	17 (3)	28 (6)
Present study	1990	24/27	18 (7)	6 (3)	

Figures in brackets are the numbers of patients considered to be improved at 3 months.

* This series has not been used in the cumulative response. The 20 MS patients in Ewing's 1982 series are assumed to be included in the 1983 series.

† This is the number improved at 6 months (all others are 3 months).

sensitive and post-operative) are tabulated in Table 1.

Our results parallel those of the most recent studies (Nordling *et al.*, 1986; Wall and Stanton, 1989; Rosenbaum *et al.*, 1990) in suggesting that the benefit of transvesical phenol injection is short-lived, with only 2 of 18 patients with detrusor instability having any improvement at 6 months. Our hyper-reflexic group is small but does seem to include the occasional long-lived successful treatment. A possible indication for this therapy may be found in the subgroup of patients with long-term catheters where bypassing is a problem, as demonstrated by one of our patients and emphasised by the report of Murray *et al.* (1986), where 7/83 patients in this category remained improved at 1 year later.

The overall complication rate against which this degree of success must be balanced is 11% (Table 2)

Table 2 Documented Complications in 318 Patients Undergoing 370 Extravesical Phenol Injections

Complications	No. (%)
Chronic retention of urine	11 (3)
Acute retention of urine	10 (2.7)
Fistula formation	6 (1.4)
Significant haematuria	5 (1.3)
Sciatic nerve palsy (transient)	2
Trigonal ulceration	2
Ureteric reflux (transient)	2
Ureteric reflux (permanent)	1
Ureteric stenosis	1
Periurethral fibrosis	1
Vesical calculus	1
Total	42 (11.3)

(some of these have already been detailed above in the case reports). The complications which ensue are the consequence of tissue damage resulting in marked tissue fibrosis around the base of the bladder and associated structures including the bladder neck, urethra and ureters. Three patients developed rigid urethras as a consequence of periurethral fibrosis; only one of these patients had undergone previous surgery to the bladder neck and in this case functional reconstruction of the urethra was not possible. Transient ureteric reflux has been described previously (Ewing *et al.*, 1982) but not permanent reflux or ureteric stenosis, both of which occurred in one of our patients.

In more extreme cases tissue damage may result in tissue necrosis (fistulae) and other workers have also reported the development of fistulae (Nordling *et al.*, 1986; Cameron-Strange and Millard, 1988; Wall and Stanton, 1989). Predisposing factors include tissue ischaemia and scarring resulting from previous surgery or radiotherapy and second doses of sclerosant. This was clearly demonstrated in a study where ethanol was used instead of phenol but where fistulae developed in 3/10 patients—in 2 following prior radiotherapy and in 1 following injection of 230 ml of sclerosant (Harris *et al.*, 1988).

Although neural damage is the aim of this therapy, the difficulty of accurately titrating and confining the delivery of phenol to the area of the paravesical plexus has been demonstrated by Rosenbaum *et al.* (1990). Urinary retention is a recognised complication of the procedure and is almost desirable if unstable contractions are abolished (Ewing *et al.*, 1982) and symptoms relieved, but becomes in itself clinically significant if it

results in the patient being unable to produce a voluntary contraction (Cox and Worth, 1986), as in case 5. Local spread of phenol away from the perivesical area may result in severe associated neural damage, including partial sciatic nerve palsy (Blackford *et al.*, 1984) and impotence (McInerney, 1991). In addition, the systemic absorption of phenol is not without danger; multifocal ventricular ectopia has been reported after transtrigonal injection (Forrest and Ramage, 1987). Finally, there is the unusual complication of eye injuries occurring in medical staff from phenol splashing (Cameron-Strange and Millard, 1988).

Our experience confirms the growing weight of evidence in the literature to suggest that transtrigonal phenol injection has little part to play in the management of the unstable bladder. This report emphasises the small yet significant incidence of severe side effects which accompany this therapy, particularly in patients who have undergone previous surgery or radiotherapy. We would therefore suggest that this therapy should be dropped from routine use, although it may still be of use for the patient with refractory hyper-reflexia and in highly selected cases of detrusor hypersensitivity where all else has failed. The use of repeated injections should be avoided because of the increased risk of complications.

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Clam Ileocystoplasty

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Summary—Clam enterocystoplasty has been used successfully in the treatment of refractory urge incontinence. We report 31 patients who underwent ileocystoplasty between 1982 and 1989. The majority of patients were pleased with the outcome of the operation. The main post-operative complication was voiding dysfunction due to relative bladder outflow obstruction. Urinary tract infection and mucus production were significant long-term problems.

The past decade has seen an increasing use of bowel either for augmentation or substitution cystoplasties in various bladder pathologies (Ashken, 1982). The technique of clam enterocystoplasty was first described by Bramble (1982) for refractory urge incontinence. Bramble initially used sigmoid colon but later used a distal segment of ileum, which is more suitable for the technique.

The procedure comprises opening the bladder like a clam, with four-fifths of the bladder segment posterior and one-fifth anterior. It is important to extend the incision close to the ureteric orifices (Fig.). This gives a good bivalving of the bladder and prevents the formation of a pseudodiverticulum. A measured segment of distal ileum (about 15 cm) is isolated and opened on its antimesenteric border over a chest tube drain within the lumen of the ileum, using a diathermy point which reduces the bleeding from the cut edges. The detubularised segment is sewn into the bladder using short runs of 2/0 Dexon sutures. In older women the pedicle is brought anterior to the broad ligament whilst in the younger female patient the pedicle is passed posterior to the broad ligament. This reduces the risk of damage to the pedicle should any subsequent obstetric or gynaecological surgery be necessary.

We present our experience with clam enterocystoplasty in 31 patients during a period of 7 years.

Patients and Methods

Since 1982, 31 patients have had a clam enterocystoplasty. The series included 30 females and 1 male, aged between 22 and 83 years (mean 51). Follow-up ranged from 6 months to 7 years (average 4 years).

A total of 28 patients were operated on for urge incontinence associated with detrusor instability. All had pre-operative urodynamic evaluation that showed detrusor instability. Three patients underwent surgery for other reasons: 1 had a small

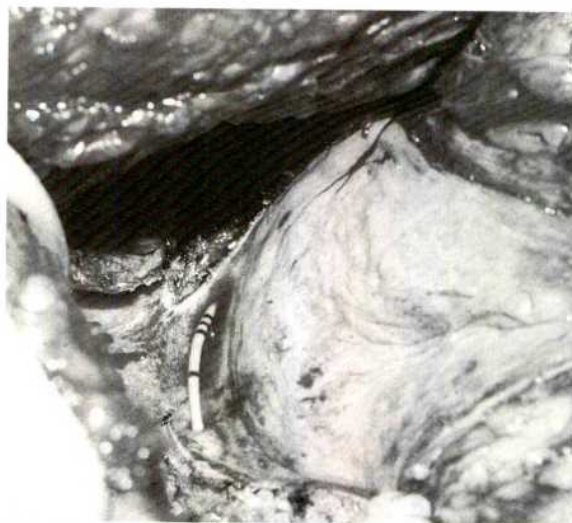


Fig. Bladder opened like a clam with ureteric catheter inserted into ureteric orifices.

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capacity bladder following radiation and 2 had interstitial cystitis.

All patients with instability had anticholinergic treatment that failed to control their symptoms; 15 had hydrostatic/Helmstein distension and 4 had endoscopic transection of the bladder. About half of the patients (12/28) dated their symptoms from hysterectomy.

Results

Twenty patients with instability are free of urgency and urge incontinence following clam ileocystoplasty. In the other group (interstitial cystitis 2; 1 small capacity irradiated bladder) all are symptom-free. The pre-operative urodynamic assessment showed 10 patients with poor compliance and the bladder capacity ranged from 100 to 360 ml (mean $220 \text{ ml} \pm \text{SD } 82.39$). Twenty-two patients underwent urodynamic evaluation following enterocystoplasty; 17 had a stable detrusor but instability persisted in 5. All had pressure $> 65 \text{ cm H}_2\text{O}$ with the abnormal detrusor contractions in the pre-operative urodynamic study. Bladder capacity after operation was between 260 and 550 ml (mean $448 \text{ ml} \pm \text{SD } 92.14$), which was highly significant ($p < 0.0001$) and 11 patients had residual urine $> 150 \text{ ml}$.

One patient who was 80 years old died on the tenth post-operative day as a result of pulmonary embolus. Two patients were re-explored, 1 for bleeding and the other for small bowel obstruction. Wound infection developed in 2 patients.

Late complications included 17 patients with voiding dysfunction probably due to their relative outflow obstruction after clam ileocystoplasty. Nine patients were troubled with mucus production associated with chronic urinary tract infection. One patient had a fistula and 2 had incisional hernias. Ten patients improved and became asymptomatic after anticholinergic medication or Otis urethrotomy. Six patients are on clean intermittent self-catheterisation and find their present state preferable to the pre-operative one; 3 patients find self-catheterisation easy but the other 3 accept it with some reluctance. One patient has an indwelling urethral catheter.

Discussion

Clam enterocystoplasty is an effective method of treatment for refractory cases of urge incontinence. This method is also advocated for some neuropathic bladders (McRae *et al.*, 1987) and as a form of

substitution cystoplasty (Mundy and Stephenson, 1985). In the present study, 23 patients improved and are free of symptoms of urge incontinence.

Voiding dysfunction remains a common problem after any type of augmentation or substitution cystoplasty. This is caused by relative outflow obstruction due to the low pressure cystoplasty and is particularly important in male patients, where unilateral endoscopic bladder neck incision may be necessary (Mundy and Stephenson, 1985). The one male patient in this series who underwent enterocystoplasty was only 29 years old; therefore a bladder neck incision was not done and he has no voiding problems. It is recommended that these patients are given pre-operative training for clean intermittent self-catheterisation.

Urinary tract infection developed in about one-third of patients. The optimal pH for growth of pathogenic bacteria in a urinary tract is 6–7. In recent tests we found that the average pH measured in 24-h urine samples in enterocystoplasty patients was 6.77 in 18 samples.

The mucin which is present in the urine in these patients is an important carbohydrate-containing source of energy for bacterial growth. Thus the increase in pH, the presence of mucus and incomplete emptying due to relative outflow obstruction predispose to urinary tract infection. In these patients with high pH, vitamin C is recommended to lower the pH and to reduce the chance of urinary infection.

Mucus is a high molecular weight glycoprotein containing 50 to 70% of carbohydrate arranged in the form of a chain around a central protein core. We have found that the average mucus content in urine in patients with enterocystoplasty is $2.76 \pm 0.36 \text{ g/day}$. When this mucus is precipitated it can exacerbate the bladder outflow obstruction in an already low pressure system, leading to chronic retention of urine and infection. A trial conducted to assess the effect of ranitidine on mucus production in these patients showed a marked reduction whilst they were on the drug.

Another matter of concern is the long-term incidence of carcinoma in the ileal segment used for cystoplasties, with 9 cases reported to date (Stone *et al.*, 1987; Filmer and Spencer, 1990). The majority of these patients died of widespread metastasis despite local excision of the tumour. It is therefore important to have a long-term endoscopic follow-up of these patients.

In conclusion, clam ileocystoplasty is a simple and effective method of treatment for all patients with refractory urge incontinence and it can also be

used as a form of substitution cystoplasty. Careful follow-up is essential to identify outflow obstruction leading to chronic retention and urinary tract infection. There are encouraging early results using Ranitidine to lower the mucus in urine in patients with enterocystoplasty. Carcinoma remains a rare but worrying complication in the cystoplasty.

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Neoadjuvant Chemotherapy with Methotrexate and Cisplatin prior to Radiotherapy for Invasive Transitional Cell Carcinoma of the Bladder. Assessment of Feasibility and Toxicity

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Summary—A prospective study has been performed to assess the feasibility and toxicity of administering neoadjuvant chemotherapy with methotrexate (200 mg/m²) and cisplatin (100 mg/m²) prior to radical radiotherapy. Twenty patients with advanced transitional cell carcinoma of the bladder were assessed after each of 3 courses of chemotherapy, after radiotherapy and 6 months following treatment. Of particular concern was whether neoadjuvant chemotherapy compromised the ability to give potentially curative radical radiotherapy, delayed effective palliation of distressing urinary symptoms, or allowed local tumour progression prior to definitive treatment.

It was concluded that this chemotherapy regimen was well tolerated, did not compromise the ability to give radical radiotherapy and resulted in the prompt palliation of urinary symptoms. This treatment, however, did not stop the development or progression of metastatic disease in some patients. In only 1 patient was there local progression during chemotherapy.

The prognosis for patients with muscle-invasive bladder cancer has not changed materially over the last 10 to 15 years, with approximately one-third of patients surviving 5 years (Duncan and Quilty, 1986). There have been many attempts to improve the outlook for such patients, including novel local treatments and systemic therapy. There are now numerous reports of the activity of mainly cisplatin-containing chemotherapy regimens for what used to be considered a chemoresistant tumour. The response rate and duration of response to single agent chemotherapy have always been disappointing, but combination regimens such as methotrexate and cisplatin (Carmichael *et al.*, 1985), and methotrexate, vinblastine, doxorubicin and cisplatin (Sternberg *et al.*, 1988) now offer better overall response rates well in excess of 50%. It is still impossible to assess what impact these regimens may have on survival.

The primary management of bladder cancer in

Edinburgh, as in many other centres in the UK, is radiotherapy, reserving surgery for residual or recurrent disease. With the advent of effective chemotherapy for a disease where possibly 50% of patients relapse at distant sites (Timmer *et al.*, 1984), interest has naturally moved to its use in an adjuvant setting. There has been great concern over the toxicity of chemotherapy in this group of elderly patients, but few studies have assessed the toxicity of the combination of chemotherapy and radiotherapy. The delay of radiotherapy by 2 or more months may allow local tumour progression and delay effective palliation of troublesome urinary symptoms. Of particular importance is the question of whether the ability to give potentially curative treatment is compromised by this approach.

The combination of methotrexate and cisplatin has been used for several years in Edinburgh for metastatic disease (Carmichael *et al.*, 1985). This prospective study was designed to assess the feasibility of using this regimen in a neoadjuvant setting. Particular emphasis has been put on the

accurate assessment of toxicity and urinary symptoms. Survival data are difficult to interpret in a small non-randomised study of this sort. Response has, however, been formally assessed after the third course of chemotherapy, after the combined treatment and at 6 months.

Patients and Methods

Patients considered for entry into the study were those newly diagnosed as having either T3 or T4 NO MO (UICC, 1978) transitional cell carcinoma (TCC) of the bladder. Three patients with suspected metastatic disease were included as local radiotherapy to the bladder was still considered to be appropriate.

Initial staging was performed jointly by a urological surgeon and an oncologist. A bimanual examination was performed before and after transurethral resection. The tumour was debulked and quadrant mucosal biopsies taken as well as a biopsy from the tumour base. All pathological specimens were reviewed by a single pathologist. Further staging investigations included a full blood count, serum electrolytes and liver function tests, creatinine clearance, chest X-ray, CT scan of the pelvis and abdomen and a bone scan. Consenting patients were then to receive 3 courses of chemotherapy with methotrexate 200 mg/m² in 1L normal saline infused over 24 h with folinic acid rescue (15 mg 6-hourly iv $\times$ 4 and 15 mg 6-hourly orally $\times$ 4). The methotrexate was followed by cisplatin 100 mg/m² in 500 ml 10% mannitol given over 1 h. A pre-hydration regimen ensured a urinary output > 100 ml/h during administration of cisplatin. This 3-day regimen was repeated every 21 days to a total of 3 courses. Criteria for dose reduction were strictly observed. The full dose was prescribed only with a creatinine clearance > 100 ml/min. The dose of both drugs was reduced to 75% and 50% of the total with creatinine clearances of 75 to 99 ml/min, and 50 to 74 ml/min respectively. Extended folinic acid rescue (12 oral doses of 15 mg) was prescribed with clearances of 50 to 74 ml/min.

Radiotherapy was commenced 3 weeks after the third course of chemotherapy. A standard 3-field technique was performed which has been described in detail by Duncan and Quilty (1986). A dose of 5250cGy given in 20 fractions in 26 days was prescribed to the isocentre. The volume was designed to cover the bladder and tumour alone. A 10 $\times$ 10 $\times$ 10 cm volume defined at the 50% isodose was adequate in all but 4 cases, where marginally larger fields were necessary.

Table 1 Scoring of Bladder Symptoms

Grade	
0	No bladder symptoms.
1	Microscopic haematuria only. Slight epithelial atrophy. Minor telangiectasia.
2	Moderate frequency. Intermittent macroscopic haematuria. Generalised telangiectasia.
3	Severe frequency and dysuria. Frequent haematuria. Severe generalised telangiectasia. Reduction in bladder capacity (< 150 ml).
4	Necrosis. Contracted bladder (capacity < 100 ml). Severe haemorrhagic cystitis.
5	Death directly related to radiation-induced effects.

This scoring system is based on the RTOG/EORTC system for scoring late radiation reactions. It should be noted that here it was used to assess symptoms due to bladder cancer during chemotherapy as well as including mucosal appearances at the time of follow-up cystoscopies.

The following factors were assessed prospectively, before treatment, at the time of admission for each course of chemotherapy, 1 month after the combined treatment and 6 months later:

- (1) Performance status (WHO, 1979).
- (2) Urinary symptoms (Table 1).
- (3) Gastrointestinal symptoms (WHO, 1979).
- (4) Renal and haematological toxicity as assessed by serum urea and electrolytes, full blood count and creatinine clearance. Neurotoxicity and hair loss (WHO, 1979).

Response to treatment was assessed cystoscopically, by bimanual examination (2 observers) and with a CT scan of the abdomen and pelvis. Assessments were performed after the third course of chemotherapy, 1 month and 6 months after radiotherapy. A complete response was defined as the disappearance of all disease and no evidence of malignancy in biopsy specimens. A partial response was defined as 50% reduction in maximum tumour diameter on bimanual examination and CT scanning. Any response less than this was defined as static disease. Increase in tumour size or development of new lesions at any site was considered to be progressive disease.

Results

Fifteen male and 5 female patients (median age 57 years, range 40–73) consented to be entered into this study. Details are annotated in Table 2, the majority of patients having Grade 3 T3 NO MO

Table 2 Details of Patients

	<i>No. of patients</i>
T stage	
T2	1
T3	17
T4	2
Histological grade	
Grade 1	0
Grade 2	2
Grade 3	18

TCC; 58 courses of chemotherapy were given. The dose of chemotherapy was reduced in 64% of courses, in all cases due to reduced renal function. Two courses were delayed because of prolonged myelosuppression. In 3 cases chemotherapy was suspended before completion, in 1 due to the patient's death from a myocardial infarction and in 2 due to the patients' intolerance of the side effects of treatment.

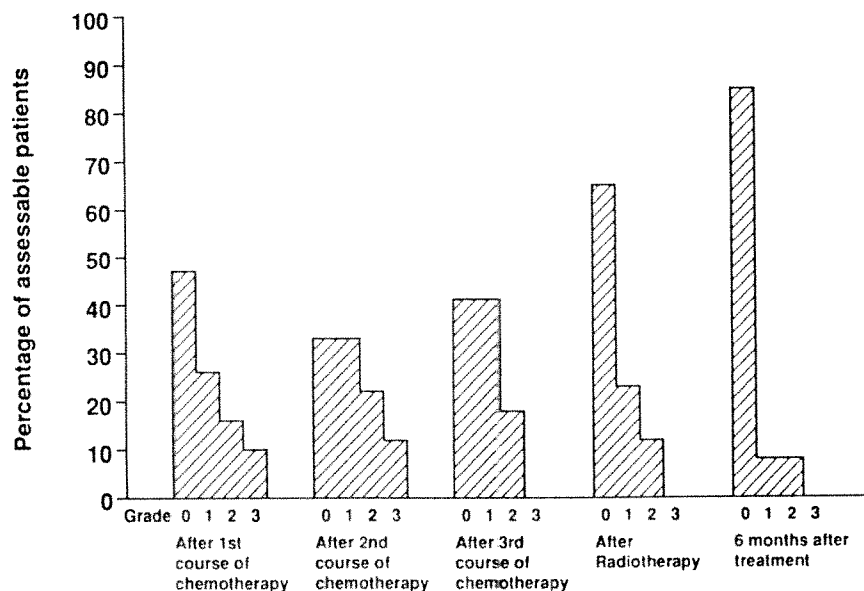
Radiotherapy was given as prescribed in 17 of 19 patients. Radiotherapy was modified in 2 patients who developed unequivocal evidence of metastatic disease. In no case did the radiotherapy have to be modified as a result of the toxicity of either the chemotherapy or the radiotherapy.

Predictably, the major side effect of both the

chemotherapy and radiotherapy was gastrointestinal. This was, however, not severe (maximum WHO Grade 3) and was not persistent (Fig. 1). Other toxicity was minimal, with haematological toxicity on 5 occasions only (maximum WHO Grade 2), no renal toxicity, hair loss in 7 patients (maximum Grade 2) and Grade 1 neurotoxicity in 3 patients. It is worth noting that although a dose reduction was necessary in the majority of patients because of poor renal function, no deterioration in renal function was documented during treatment. The 2 patients who failed to complete 3 courses of chemotherapy because of toxicity complained of general malaise rather than marked severity of any particular side effect.

Bladder symptoms improved during chemotherapy in all cases, with the majority of patients having complete relief of symptoms after the third course (Fig. 2). This was reflected as an improvement in performance status in most cases (Fig. 3).

One patient died of a myocardial infarction after 1 course of chemotherapy. Response was therefore assessable in 19 patients, of whom 9 demonstrated a response, either complete or partial, to chemotherapy alone. One month after radiotherapy this was increased to 12, with 3 complete responses. At 6 months, the time when normally the first check cystoscopy would be performed, it was possible to

**Fig. 1** Gastrointestinal toxicity during and after treatment.

Numbers of patients assessable:

Before treatment	19	After 3rd course of chemotherapy	17
After 1st course of chemotherapy	19	After combined treatment	17
After 2nd course of chemotherapy	18	6 months after treatment	13

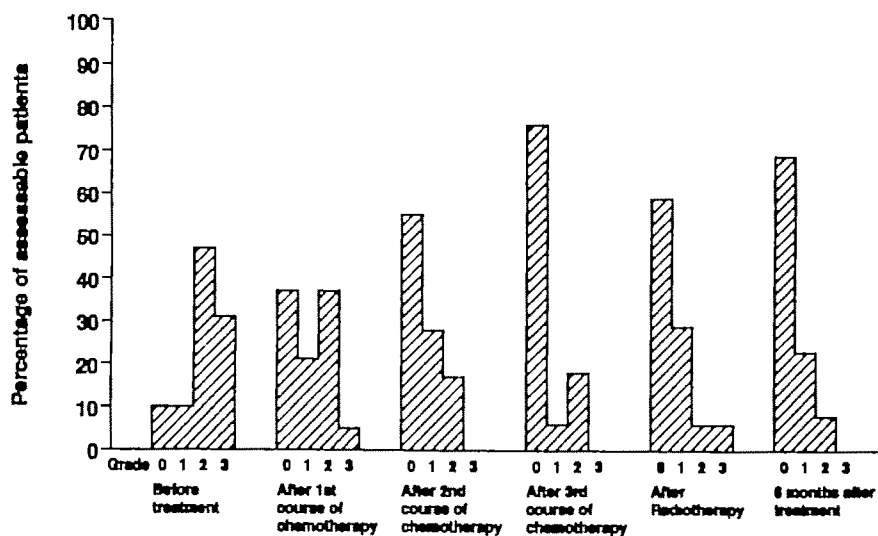


Fig. 2 Bladder symptoms during and after treatment.

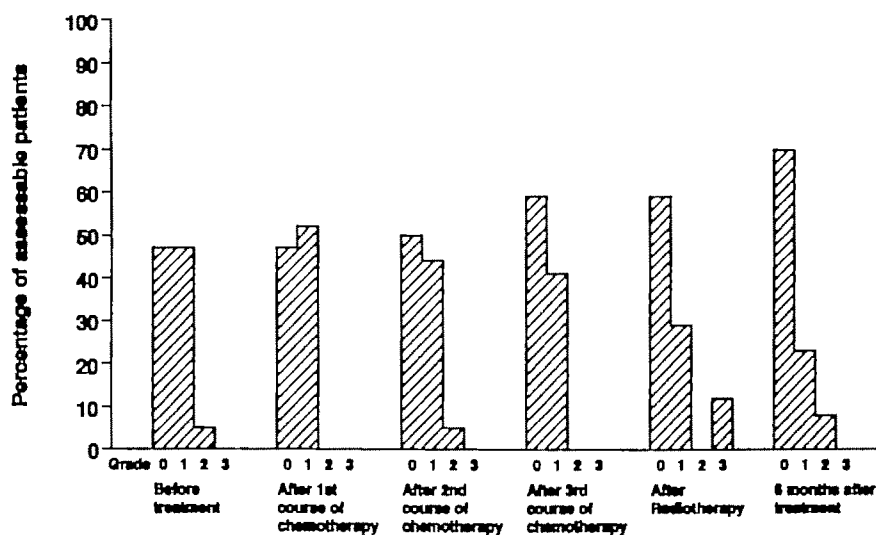


Fig. 3 Performance status during and after treatment.

assess 13 patients, 6 more having either died or developed metastatic disease. Four patients had no evidence of disease and a further 3 achieved a partial response. The overall response rate was 37% (Table 3).

There was disease progression in 3 patients during chemotherapy, 1 locally and 2 at metastatic sites. The latter 2 patients had equivocal radiological evidence of metastatic disease at the outset of treatment. Five patients had progressive disease after radiotherapy, 4 locally and 1 metastatic.

All but 1 patient who had progressive disease on chemotherapy have subsequently died, whilst 4 of 9 of those patients who responded to chemotherapy

Table 3 Response to Treatment

	After chemotherapy	After radiotherapy	6 months after treatment
CR	1 (5%)	3 (16%)	4 (21%)
PR	8 (42%)	9 (47%)	3 (16%)
SD	6	0	0
PD	3	5	6

CR = Complete response. PR = Partial response. SD = Stable disease. PD = Progressive disease.

are disease-free with a minimum follow-up of 6 months.

Of the 12 patients who relapsed, 4 had a salvage cystectomy for local relapse alone. Three of these patients remain alive with no evidence of disease, the fourth dying of metastatic disease. Nine patients relapsed with metastatic disease, the sites being lung (2), bones (3), intra-abdominal or pelvic nodes (3) and skin (1).

Discussion

This study was designed to assess the toxicity and feasibility of combining chemotherapy and radiotherapy in the treatment of poor prognosis TCC of the bladder. It would be of concern if the unproven benefits of neoadjuvant chemotherapy were to compromise the ability to give definitive treatment, in this case radiotherapy. It should be noted that late radiation toxicity has not been formally assessed as the final 6-month assessment is too early for this.

The chemotherapy regimen documented here incorporates relatively high doses of methotrexate and cisplatin but with strict dose reduction criteria. It is of note that although the majority of patients required dose reductions because of poor renal function, the regimen was well tolerated. Gastrointestinal toxicity was the most marked but this was generally mild and not prolonged. The prompt improvement in urinary symptoms following chemotherapy was encouraging, indicating that delaying effective palliative treatment in the form of radiotherapy was not detrimental to the patients' quality of life. After chemotherapy there was locally progressive disease in 1 patient. In this patient there was continued progression during radiotherapy and we feel that the delay in starting radiotherapy was not detrimental. The ability to prescribe and give radical radiotherapy was not compromised in any way by prior chemotherapy.

Few conclusions can be drawn from the response to treatment in a small feasibility study. A number of features are, however, apparent. Neoadjuvant chemotherapy with this regimen did not prevent the development of metastatic disease in 9 patients. The failure to respond locally to chemotherapy would appear to be a poor prognostic sign, with all but 1 patient subsequently dying of disease. Conversely, a response to chemotherapy is suggestive of a good prognosis, with 55% of those patients being disease-free at 6 months.

We concluded that this chemotherapy regimen is well tolerated and offers effective palliation of

urinary symptoms. It does not compromise the ability to give radical radiotherapy but does not prevent the development of metastatic disease. These conclusions may not, however, apply to different chemotherapy regimens which may have a greater radiosensitising effect, or other radiotherapy protocols which may involve larger fields and higher doses. A documented response to chemotherapy would appear to be a good prognostic indicator. Whether or not neoadjuvant chemotherapy has any effect on survival is currently being assessed in a large randomised trial under the auspices of the Medical Research Council.

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How Effective is Topical Alpha-2b Interferon in Preventing Recurrence of Superficial Bladder Cancer?

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Summary—A total of 44 patients with low and intermediate grade superficial urothelial bladder cancer Ta and T1 were randomised into a controlled, long-term, phase III trial on topical instillation therapy with high dose alpha-2b interferon (100×10^6 IU *versus* low dose alpha-2b interferon (10×10^6 IU) *versus* ethoglucid. Thirteen patients in the low dose group, 11 in the high dose group and 10 in the ethoglucid group completing the trial were evaluable (median follow-up 36.5 months) and were followed up for 3 years. They were treated weekly for 10 weeks and then monthly for a total of 1 year. The aim of the trial was to establish the prophylactic efficacy and the toxic side effects, if any, of alpha-2b interferon in the topical treatment of superficial bladder cancer. Recurrence rate and disease-free survival were chosen as study end-points. The recurrence rate was 4.4 in the low dose interferon group, 2.76 in the high dose interferon group and 3.08 in the ethoglucid group. In the low dose interferon group the time to the first recurrence was 22.23 months *versus* 22.36 in the high dose group and 21.76 months in the ethoglucid group. No differences of statistical significance were noted between the 3 groups. Progression occurred in 5 patients on interferon but was not seen in those on ethoglucid. Neither systemic nor local side effects were seen in the interferon groups, but 3 patients had to be taken off ethoglucid because of severe chemocystitis. In superficial bladder cancer, topical instillation therapy with interferon is as effective as conventional chemotherapy and has no side effects.

The close association between bladder cancer and modulation of the immune system has been known for years. Reactivity to surface antigens, *e.g.* the ABO blood type and T-group antigens, is often lost with the development of bladder cancer (Kovarik *et al.*, 1968; Coon *et al.*, 1982; Sadoughi *et al.*, 1982). These findings and the accessibility of the bladder mucosa to direct topical treatment permitted and justified an immunotherapeutic approach to bladder cancer.

Bacillus Calmette-Guérin has had a firm place in the treatment of superficial bladder cancer for many years. Experimental and clinical findings showed BCG therapy to stimulate circulating interferon levels (Catalona *et al.*, unpublished data). However, it is uncertain whether increased levels of circulating interferons are responsible for any of the

cytotoxic, cytostatic or immunomodulatory actions of BCG (Torti and Lum, 1986). Non-recombinant and recombinant interferon was used in different modes of application for superficial bladder carcinoma (Ikic *et al.*, 1981; Kemeny *et al.*, 1981; Scorticatti *et al.*, 1982; Torti *et al.*, 1984). Borden *et al.* (1984) showed the antiproliferative effects of interferon on human bladder carcinoma cell lines to be dose-dependent. They also found a clear correlation between exposure times and inhibitory effects on cell growth (Denz *et al.*, 1985). These results suggested that interferon may have a place in the treatment of superficial bladder cancer.

Prompted by these phase I and II studies, a controlled randomised phase III trial was designed comparing high dose interferon with low dose interferon and ethoglucid to define the potential of topical interferon in preventing recurrent superficial bladder cancer.

Patients and Methods

E. coli-derived recombinant alpha-2b interferon was used (Intron A®, Sherring, Kenilworth, USA). Patients were eligible for the study if they had histologically documented primary grade 1 or 2 papillary transitional cell carcinoma of the bladder stages Ta, T1 or Tis or if they had recurrent grade 1 tumour stages Ta or T1. They had to have complete resection of all visible tumour tissue followed by multiple random biopsies at the end of transurethral resection (TUR). Patients who had received intravesical or systemic chemotherapy or immunotherapy previously, as well as those with a history of other malignancies except non-metastatic skin cancer, were excluded. Pelvic irradiation within the previous 3 months was another exclusion factor. Patients were required to have a Karnofsky performance status of 50% or greater, adequate renal function (creatinine ≤ 2.5 mg%) and hepatic function (bilirubin ≤ 1.2 mg%), a total white blood cell count $\geq 2500/\text{mm}^3$ and a platelet count $\geq 100\,000/\text{mm}^3$. Informed consent was obtained.

A total of 44 patients were admitted to the trial (Table 1). Treatment was started within 36 h after complete TUR of all tumour tissue. Interferon was instilled into the bladder through a catheter at a dose of 100×10^6 IU (high dose group) or 10×10^6 IU (low dose group) dissolved in 30 ml of sterile pyrogen-free water once weekly for 10 weeks and then monthly for 1 year. Ethoglucid, 1.13 g dissolved in 100 ml of sterile pyrogen-free water, was instilled into the bladder once weekly for 10 weeks and then monthly for 1 year. Cystoscopy and

cytology were performed in all patients before initiation of therapy and prior to the instillations at 3, 6, 9 and 12 months.

During the 12-month treatment period, transitional cell carcinoma (TCC) recurrences (except grade 3 tumours or muscle invasion) were resected and patients were continued on instillation therapy.

Patients with evidence of progressive disease during the treatment period were dropped from the study and regarded as treatment failures. Patients who were disease-free or had their first recurrent tumour at 12 months were followed up for recurrence or progression every 3 months for 1 year and then at 6-monthly intervals for at least another 2 years. Toxicity was assessed following each instillation course. Routine haematology, serum chemistry and urine cultures were done weekly for 4 weeks and then every month.

Statistical evaluation

Curves of survival and time to first progression were estimated by the Kaplan-Meier method (Kaplan and Meier, 1958). Significance levels were assessed by the generalised Wilcoxon (Breslow) and Savage (Mantel-Cox) tests. For statistical analyses the BMDP software package, University of California, was used.

Results

A total of 34 patients were available for evaluation of response; 8 were lost due to non-compliance and 2 died from unrelated causes (stroke, myocardial

Table 1 Data on Patients Available for Evaluation of Response

	Group I (low IFN) (n = 13)	Group II (high IFN) (n = 11)	Group III (ethoglucid) (n = 10)
Median age in years (range)	68.1 (52-84)	67.7 (44-85)	72.6 (61-89)
Males	10	5	6
Females	3	5	4
Primary tumour	6	4	5
Recurrent tumour	7	7	5
No. of tumours			
Single	7	4	5
Multiple	6	7	5
Tumour grade			
1	10	8	7
2	2	2	2
3	1	1	1
Tumour category			
pTa	1	—	1
pT1	11	10	8
Tis	1	1	1

Table 2 Response to Treatment

	IF low dose (10×10^6 IU)	IF high dose (100×10^6 IU)	Ethoglucid
Patients available for evaluation of toxicity (n = 44)	14	14	16
Patients available for evaluation of response (n = 34)	13	11	10
Drop-out rate (n = 10)	1*	3†	6‡
Recurrence rate	4.4	2.76	3.08
No. of recurrences/group	20	12	11
Patients free of recurrence (%)	6 (46.2)	6 (54.5)	4 (40.0)
Time to recurrence (months)	22.23	22.36	21.76
Confidence limit (95%)	11.0–41.1	8.2–43.4	8.6–36.3
Mean follow-up time in months (range)	34.9 (8–52)	37.7 (3–52)	37.2 (6–52)

* Non-Hodgkin lymphoma (1 patient)

† Stroke (1 patient), non-compliance (2 patients).

‡ Myocardial infarction (1 patient), non-compliance (2 patients), severe chemocystitis (3 patients).

infarction). The mean follow-up time was 36.5 months (range 3–52) (Table 2). Results were calculated by recurrence rates. These were defined as ratios between the number of recurrent tumours and the number of follow-up months multiplied by 100:

$$RR = \frac{\text{no. of recurrences}}{\text{no. of follow-up months}} \times 100$$

Recurrence rates and times to first recurrence for each group are listed in Table 2. Neither the Wilcoxon nor the Mantel-Cox test showed any significant differences in terms of the number of and time to recurrences ($P=0.92$; $P=0.93$). Progression was defined as recurrence of TCC grades 2 and 3, as disease stage T2 or more, or as metastatic disease.

No systemic side-effects were seen in any of the groups. There was no local toxicity such as chemocystitis or significant dysuric symptoms in the interferon groups. In the ethoglucid group, by contrast, 3 patients had to be taken off the drug because of severe chemocystitis, which explains the higher drop-out rate in this group. Progression occurred in 1 patient in the low dose interferon group at 3 months and in 4 in the high dose interferon group (2 at 3 months and another 2 at 6 months). No progression was seen in the ethoglucid group.

Discussion

The therapeutic efficacy of ethoglucid in superficial bladder cancer is well established and comparable to that of other chemotherapeutic agents used for this purpose (Kurth *et al.*, 1984). Ethoglucid was,

therefore, chosen as a reference agent in the control group. In a randomised prospective trial it was compared with alpha-2b interferon to evaluate the prophylactic efficacy of interferon as adjuvant following TUR for superficial bladder cancer.

In a phase II study of alpha-2b interferon for primary therapy (chemoresection) of superficial urothelial bladder cancer, Torti *et al.* (1988) reported a complete response in 32% of patients with carcinoma *in situ*. Of the patients with recurrent papillary tumours and prior intravesical chemotherapy, 25% showed complete remission. No severe side effects were noticed during intracavitary instillation of interferon. The maximal dose of interferon tolerated on intravesical instillation was not reached in a single case and therapeutic results were not found to be dose-dependent (Torti *et al.*, 1988). Another trial, still under way, compares low dose (10×10^6 IU) with high dose (100×10^6 IU) interferon in carcinoma *in situ* (Cis) of the bladder. Preliminary results suggest the higher intravesical dose to be more effective against Cis (Williams *et al.*, 1988). In our trial, with a mean follow-up time of 36 months, results were not significantly different in any one of the 3 groups, but the outcome in terms of remissions was better in the high dose interferon (100×10^6 IU) and the ethoglucid groups than in the low dose interferon (10×10^6 IU) group.

As with any topical chemotherapy, the mechanisms underlying the therapeutic action of topical interferon are unclear. In experimental studies both direct and indirect mechanisms were shown to be involved in the action of alpha-interferons (Balkwill *et al.*, 1982; Taylor-Papadimitriou, 1984). Interferons are able to affect malignant cells directly by their cytostatic, cytotoxic and antiproliferative or

differentiating actions, which alter cell phenotype and metabolism or inhibit important cellular genes such as oncogenes, but they also have an indirect effect on the cells of the immune system, including natural killer cells, T cells and macrophages. Human clinical trials with interferons suggested that most of the antitumour response was attributable to direct effects on tumour cells (Blalock *et al.*, 1980).

In this trial, topical treatment of superficial bladder cancer with alpha interferon proved to be effective and was devoid of local or systemic side effects. The main difference between interferon and ethoglucid was in the higher local toxicity of ethoglucid, which caused severe chemocystitis in some patients. Since interferon even in low dose applications is 10 times more expensive than ethoglucid, however, its routine use appears to be impracticable at the present time. This also explains the small number of patients in this trial. Improved manufacturing techniques for interferons may well solve this problem.

Further trials with a larger number of patients should identify those patients with superficial bladder cancer who are most likely to benefit from topical interferon treatment and establish the type of interferon best suited for a given tumour grade and stage. Concentrations and dosing intervals ensuring optimal efficacy still need to be more clearly defined. Torti *et al.*, (1988) suggested that interferon may be more potent in less well differentiated tumours and that, because of drug penetration, it may be more effective in tumours of only a few cell layers. This was also shown for intraperitoneal interferon in ovarian tumour implants (Berek *et al.*, 1985). Perhaps the combination with other cytotoxic or immunomodulatory drugs such as interleukins will improve the efficacy of interferon.

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Relationship between Clinical Stage and Histological Zone of Origin in Early Prostate Cancer: Morphometric Analysis

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SUMMARY—A detailed morphometric analysis of 96 radical prostatectomy specimens (13 clinical stage A1, 29 A2, 34 B1 and 20 B2) was undertaken to examine the relationship of zone of origin to volume, grade and extraprostatic extension of cancer.

In patients with stage A disease, transition zone (TZ) cancer (present in 81%) was significantly larger but of lower grade than peripheral zone (PZ) cancer (present in 90%). The total volume of cancer in stage A1 patients averaged 1.55 ml with 72% of TZ origin. In patients with stage A2 disease, tumour volume averaged 5.83 ml with only 57% of TZ origin. Specimens taken during transurethral resection of the prostate (TURP) revealed TZ cancer in 82% and PZ cancer either alone or with TZ cancer in 22%. The 9 patients with PZ cancer in the TURP specimen included 5 of the 11 with extracapsular extension and all 5 of those with seminal vesicle invasion.

Every patient with stage B disease had PZ cancer which, in all except 3 cases, was of significantly larger volume and higher grade than any TZ cancer (present in 43%) in the same gland. In patients with stage B cancer, total tumour volume was 5.13 ml with 91% of PZ origin.

TZ cancer tended to be well differentiated in all patients, even at large volumes, whereas PZ cancer was often moderately or poorly differentiated even at low volumes. In patients with stage B disease, TZ cancer appeared to be incidental and of no clinical importance, while in stage A patients PZ cancers were sometimes large, poorly differentiated and extended outside the prostate.

Progression of a stage A cancer seems more likely to result from PZ cancer than TZ cancer, and the finding of PZ cancer in a TURP specimen should probably preclude its classification as stage A1.

Clinical staging has been developed in an attempt to classify the pathological extent of prostate cancer, to suggest the prognosis of the patient and to serve as a guide to therapy. The staging systems used in prostate cancer classify non-palpable, incidentally discovered cancer as stage A (T0), implying that these cancers are an earlier form of the disease than small, palpable stage B (T1–2) tumours. Substage A1 should designate a less extensive cancer than A2, and B1 less than B2. Stage A1 was originally intended to indicate focal, well differentiated tumours that do not require therapy and are not likely to alter the survival rate of the patients

(Jewett, 1975). Yet in some patients with stage A1 cancer, disease does progress (Blute *et al.*, 1986; Epstein *et al.*, 1986) and in some with stage A2, it does not. Stage A2 patients, however, have been reported to be more likely to have nodal metastases than those with stage B1 and to be less likely to have well differentiated cancer in the radical prostatectomy specimens (Golimbu *et al.*, 1978).

Recent attempts to understand these apparent discrepancies have used data from morphometric analysis of radical prostatectomy specimens (Epstein *et al.*, 1988; McNeal *et al.*, 1988a, b; Wheeler, 1989; Christensen *et al.*, 1990). When combined with the concept of the zonal anatomy of the prostate as described by McNeal (1981), the

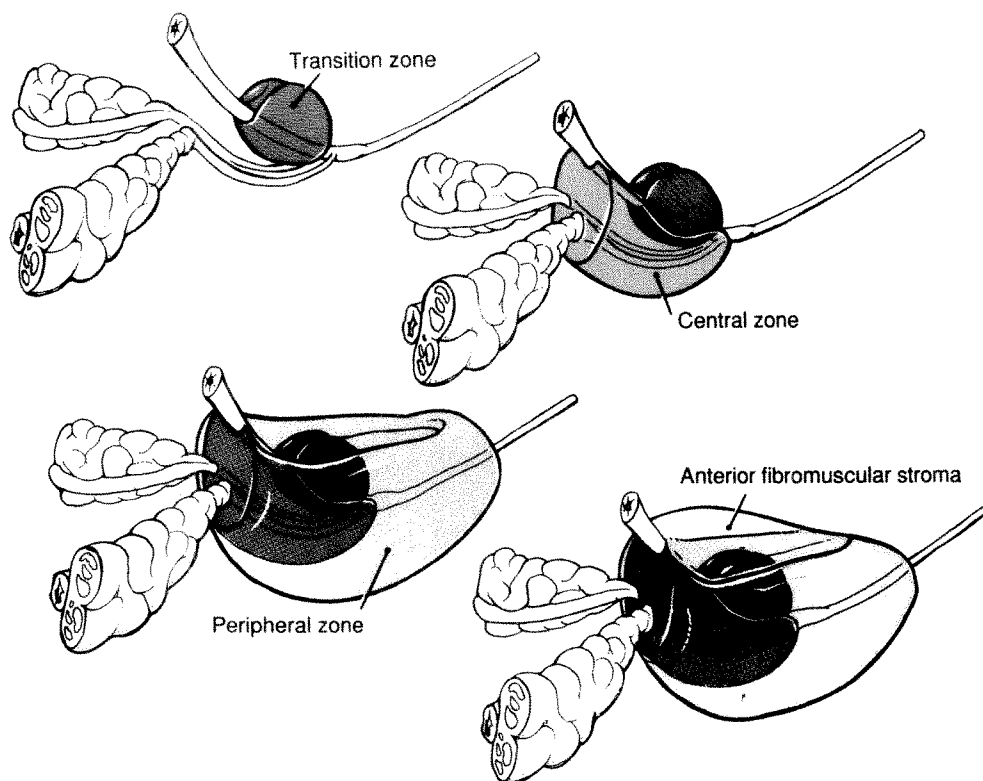


Fig. 1 Zonal anatomy of the prostate. There are 3 glandular zones and the anterior fibromuscular stroma. The transition zone comprises 10%, the central zone 25% and the peripheral zone 65% of the glandular tissue in the young adult prostate. The transition zone is the site of origin of benign prostatic hyperplasia (McNeal, 1978). In men over the age of 50 the transition zone may comprise a large proportion of the glandular prostatic tissue in marked BPH.

morphometric data offer insight into the features of prostate cancer in each clinical stage. Figure 1 illustrates the 4 regions of the prostate: 3 glandular zones and the fibromuscular stroma. The transition zone lies anteriorly and is the predominant site of origin of benign prostatic hyperplasia (BPH) (McNeal, 1978). Transurethral resection of BPH selectively samples tissue from the TZ (McNeal *et al.*, 1988a); thus stage A cancers discovered incidentally at TURP are usually of TZ origin (McNeal *et al.*, 1988b). McNeal has calculated that some 24% of prostate cancers originate in the TZ, while 68% arise in the peripheral zone and 8% in the central zone (CZ) (McNeal *et al.*, 1988b). Stage B cancers by definition are palpable and are therefore located posteriorly and are predominantly of peripheral zone origin (McNeal *et al.*, 1988a).

We have previously expressed the belief that there are distinct differences between cancers of PZ and TZ origin. Peripheral zone cancers are higher in grade and more frequently associated with extracapsular extension (ECE) and seminal vesicle invasion (SVI) (Greene *et al.*, 1990, 1991b).

We have not seen prostatic intra-epithelial neoplasia (high grade PIN, or severe intraductal dysplasia) in the TZ, but high grade PIN was present in the PZ in almost all prostates with a PZ cancer (Troncoso *et al.*, 1989; Wheeler, 1989). While most stage A cancers sampled at TURP are TZ cancers (78% in our series), almost all of our stage A patients subjected to radical prostatectomy had residual cancer in the peripheral zone (Greene *et al.*, 1991a).

McNeal *et al.* (1986) have shown a relationship between tumour volume and histological differentiation, extracapsular extension, seminal vesicle invasion and metastasis. Others have substantiated a significant correlation between tumour volume and grade (Partin *et al.*, 1989; Greene *et al.*, 1991b) and have shown that the total volume of cancer in stage A is similar to that in stage B (McNeal *et al.*, 1988a; Greene *et al.*, 1991b). We sought to examine the pathological features of prostate cancer within the PZ and TZ in each clinical substage (A1, A2, B1 and B2) to determine whether the clinical features of the disease in each stage were more closely associated with the characteristics of cancer

of PZ origin and the relative proportion of PZ cancer present than with the total volume of cancer in the prostate.

Patients and Methods

Clinical features

A series of 96 radical prostatectomy specimens was selected from prostates removed between January 1984 and July 1989 from 176 consecutive, previously untreated patients with early stage prostate cancer. These specimens were selected because the entire prostate had been step-sectioned and mapped and the original slides were available for review. In all cases a bilateral lymph node dissection had been performed before prostatectomy. Bone scan, plain radiographs and serum acid phosphatase level offered evidence that none of the patients had metastatic disease. All patients were free of nodal metastases on frozen section, but in 4 patients metastases were detected on subsequently performed permanent section.

The histological slides from each radical prostatectomy specimen and from the original TURP specimen in the 42 stage A patients were reviewed by a single pathologist (T.M.W.), who had supervised the initial preparation of the specimens. Of the 96 patients, 42 had clinical stage A disease and 54 had stage B disease. The mean age of the stage A patients was 63.4 years (range 51–74) and of stage B patients 63.0 years (range 48–78). Stage A was categorised as A1 ($\leq 5\%$ cancer in the TURP specimen or Gleason sum ≤ 7 , $n=13$) or A2 ($> 5\%$ cancer in the TURP specimen or Gleason sum > 7 , $n=29$) (Cantrell *et al.*, 1981). Stage B was categorised as B1 (1 lobe involved by tumour, $n=34$) or B2 (both lobes involved, $n=20$).

Pathological examination

The radical prostatectomy specimens were examined by a whole-organ 5-mm step-section technique previously described (Wheeler, 1989). Each separate cancer was mapped directly from a transverse haematoxylin and eosin slide (Fig. 2) and was assigned a histological zone of origin by the criteria of McNeal *et al.* (1988b). Tumours were designated as being of "transition zone" or "peripheral zone" origin. Tumours of central zone origin were assigned to the "peripheral zone" category, since these cancers are uncommon and difficult to distinguish from PZ cancers.

Cancer of TZ origin is usually well differentiated architecturally and cytologically (Fig. 3). Some of

the glands may be very large and resemble a benign gland of BPH; other glands form long channels. These 2 architectural patterns are unusual in non-TZ cancer. Cytologically, TZ cancer cells are tall and columnar in type with pale to clear cytoplasm. The single layer of minimally anaplastic nuclei is situated adjacent to the basement membrane (Fig. 3). Small TZ cancer foci frequently have a pattern of growth that is limited by the fibrous tissue boundary between the TZ and the PZ ("the surgical capsule") or the condensed stroma between adjacent BPH nodules (McNeal *et al.*, 1988b). TZ cancer has not been identified in association with prostatic intra-epithelial neoplasia (high grade PIN) (Troncoso *et al.*, 1989; Wheeler, 1989; Epstein *et al.*, 1990; Greene *et al.*, 1991b) but may appear to arise from foci of atypical adenomatous hyperplasia.

Cancer arising in the PZ may have well differentiated areas, but in clinically detectable tumours there are almost always moderately or poorly differentiated areas. PIN is almost always associated with PZ cancer and may be immediately adjacent to the cancer or mixed throughout (Fig. 2) (Troncoso *et al.*, 1989; Wheeler, 1989; Epstein *et al.*, 1990; Greene *et al.*, 1991b).

Morphometric analysis

The criteria for identification of separate cancers have been described in detail in an earlier study (Greene *et al.*, 1991a). The volume of each separate cancer focus was computed by a planimetric method using a Jandel Scientific Sigmascan program with a PC limited 286 computer. Allowance was made for the thickness of each prostate section by multiplying the measured area by 5 mm, the actual thickness of the cut sections. Because tissue shrinkage in formalin is about 10% in 1 dimension, the volume of each tumour was determined by multiplying the measured volume by a shrinkage factor of 1.33.

Forty-two patients with stage A cancer were included in the study. In 40 of these cases the TURP specimen was available for a second review to determine the probable zone of origin of the cancer. (This study updates a previous report in which 26 TURP specimens were re-examined [Greene *et al.*, 1991b]). In only 1 of the 2 instances when the TURP specimen was not obtained was TZ cancer in direct contact with the TURP defect, suggesting that this TZ cancer was sampled at TURP. In all other cases the zone of origin and

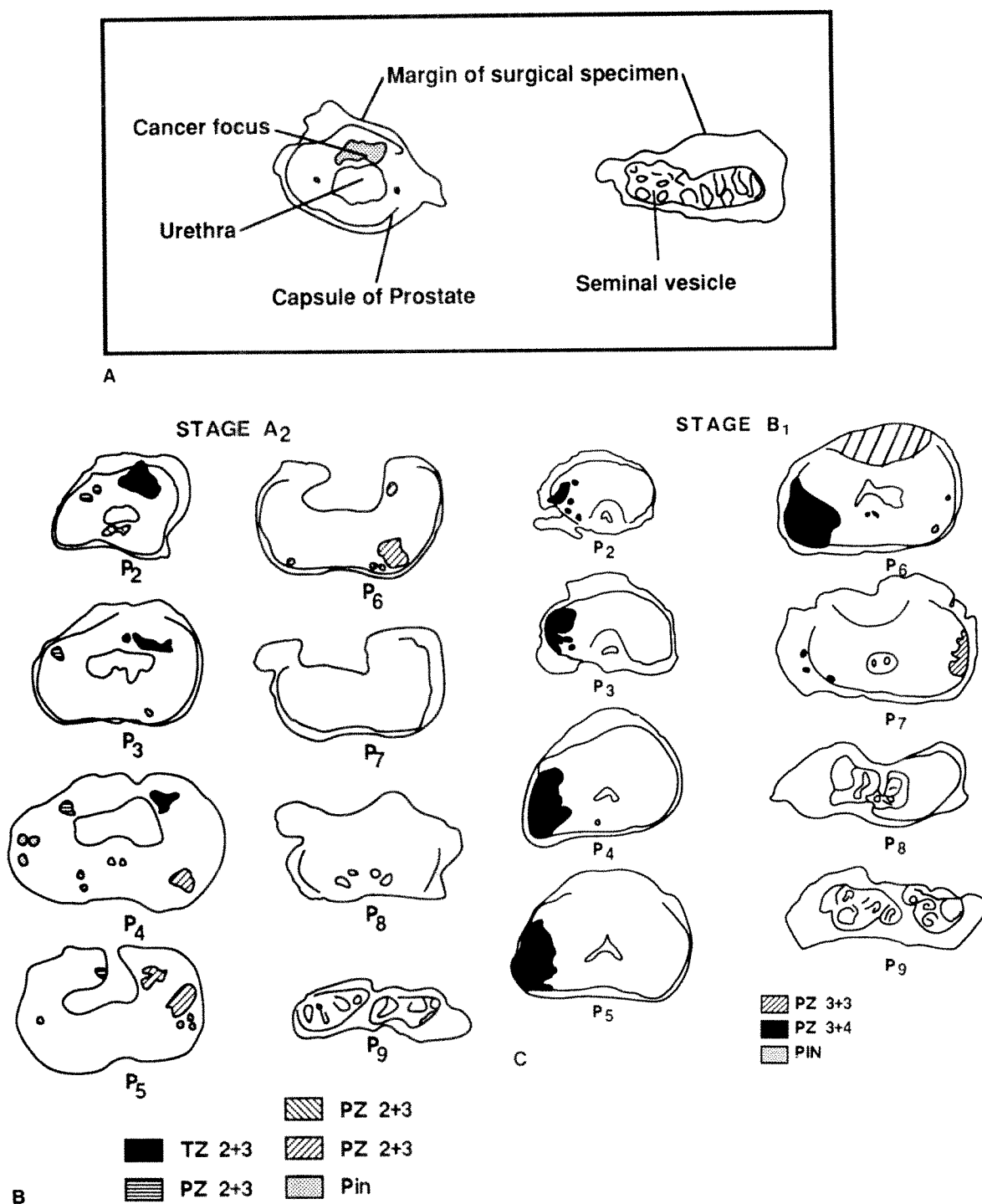


Fig. 2 (A) Tumour maps drawn from step-sectioned radical prostatectomy specimens. (B) Transition zone cancer (TZ) sampled at TURP and 3 separate residual peripheral zone (PZ) cancers with prostatic intra-epithelial neoplasia (PIN) nearby in a patient with stage A₂ prostate cancer. (C) Two separate PZ cancers with associated PIN in a stage B₁ tumour. Stage A cancers are frequently of TZ origin and located anteriorly, as opposed to stage B cancers which are usually of PZ origin and located posteriorly, but associated cancers are often present in the other zone (Greene, 1991b).

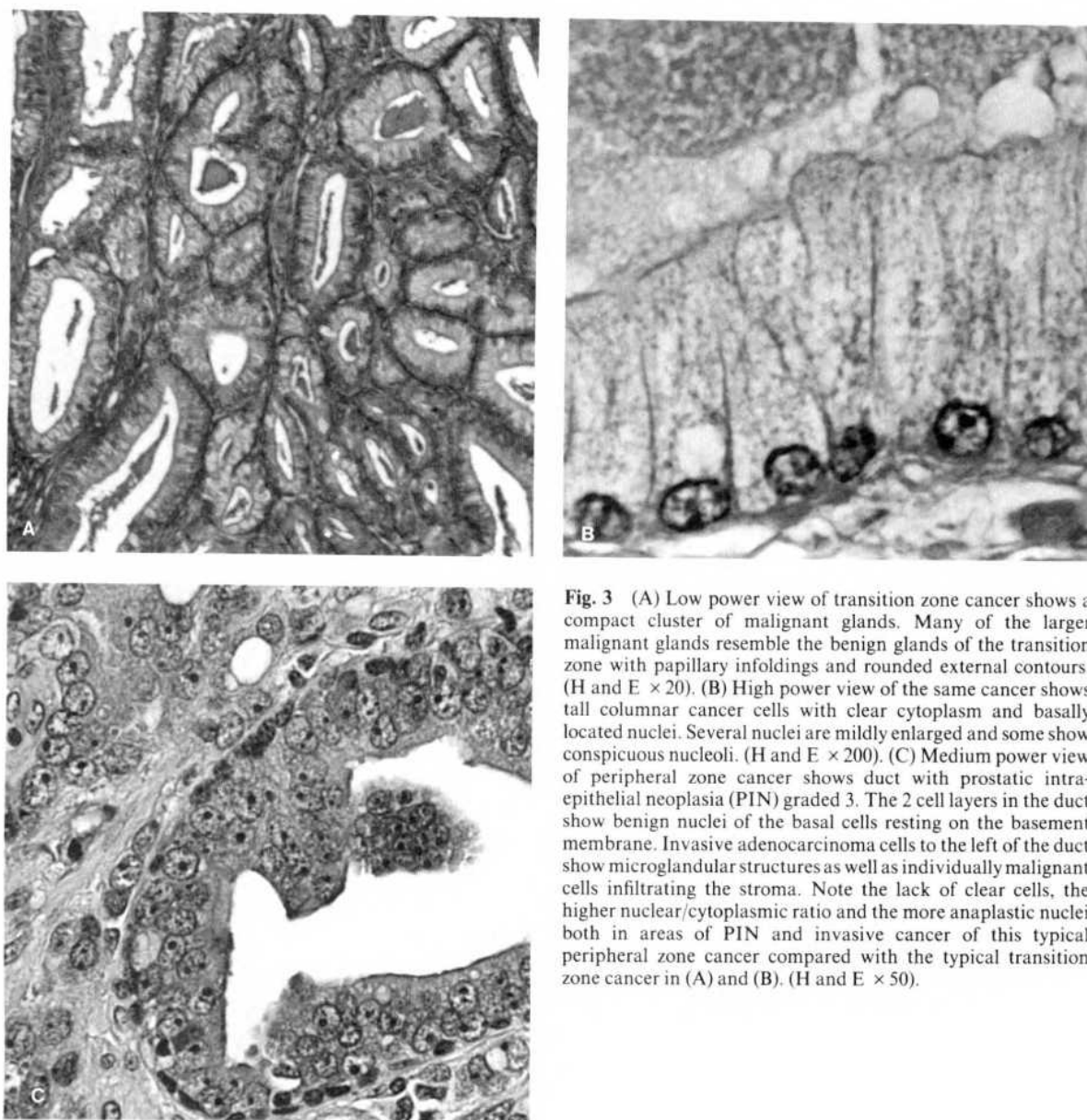


Fig. 3 (A) Low power view of transition zone cancer shows a compact cluster of malignant glands. Many of the larger malignant glands resemble the benign glands of the transition zone with papillary infoldings and rounded external contours. (H and E $\times 20$). (B) High power view of the same cancer shows tall columnar cancer cells with clear cytoplasm and basally located nuclei. Several nuclei are mildly enlarged and some show conspicuous nucleoli. (H and E $\times 200$). (C) Medium power view of peripheral zone cancer shows duct with prostatic intra-epithelial neoplasia (PIN) graded 3. The 2 cell layers in the duct show benign nuclei of the basal cells resting on the basement membrane. Invasive adenocarcinoma cells to the left of the duct show microglandular structures as well as individually malignant cells infiltrating the stroma. Note the lack of clear cells, the higher nuclear/cytoplasmic ratio and the more anaplastic nuclei both in areas of PIN and invasive cancer of this typical peripheral zone cancer compared with the typical transition zone cancer in (A) and (B). (H and E $\times 50$).

grade of cancer were compared with the zone of origin of any residual cancer in contact with the TURP defect. On the basis of these data the cancer in the TURP specimen was assigned to the transition zone, the peripheral zone or both zones according to the criteria described in McNeal *et al.* (1988b). The volume of cancer in the transition zone (or peripheral zone) in the TURP specimen was added to that in the radical prostatectomy specimen to determine the total volume of cancer in each zone of origin.

Statistical analysis was performed using the Statview 512 software package. Results are presented as the mean $\pm$ standard deviation and range; paired and unpaired *t* test analysis was used to compute significance values. Non-parametric data are presented as the median and range. Non-parametric correlation was performed using Kendall's rank correlation test (*t*), and levels of significance were computed using Wilcoxon's rank sum and signed ranks tests (Iman and Conover, 1983).

Results

More than one separate cancer was present in 34 stage A patients (81%) and the mean number of separate cancers per prostate was 3.1 (range 1–5). While 81% of these patients had a cancer of TZ origin, 90% had cancer of PZ origin. The TURP sampled cancer of TZ origin in 33 (79%), PZ origin in 7 (17%) and both PZ and TZ origin in 2 (5%). Extracapsular extension (ECE) was present in 11 patients (26%) and seminal vesicle invasion in 5 (12%).

Multifocal cancer was found in 86% of stage B patients and the mean number of separate cancers per prostate was 2.3 (range 1–5). While all stage B patients had PZ cancers, only 43% had TZ cancer. ECE was found in 34 (63%) and SVI in 13 (24%), and 4 patients (7%) had pelvic lymph node metastases on permanent section. The total volume of cancer for each patient in each substage is plotted in Figure 4.

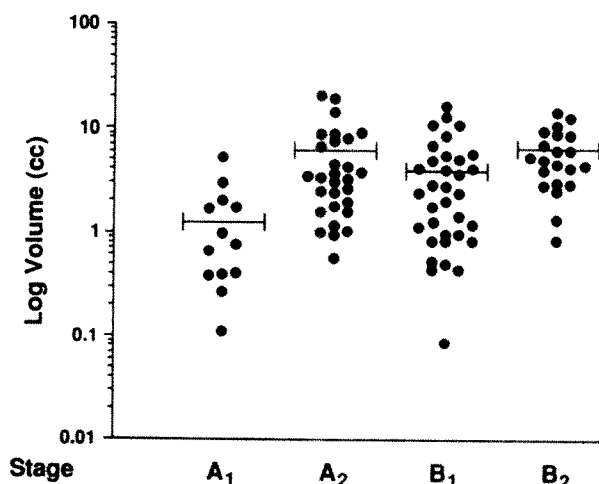


Fig. 4 The total tumour volume for each individual case is shown by substage. The mean value for each substage is represented by a crossbar (stage A1, 1.55 ml, A2 5.83, B1 3.86 and B2 6.02).

Stage A

The mean total tumour volume in patients with stage A1 cancer was 1.55 ml (Fig. 4). Eleven of these patients (85%) had TZ cancer and 12 (92%) had PZ cancer. The mean volume of TZ cancer was 1.08 ml (range 0–5.0) and the mean volume of PZ cancer was 0.43 ml (range 0–1.66) (Fig. 5A). Thus an average of 28% (range 0–100%) of the cancer present in stage A1 patients was of PZ origin.

In patients with stage A2 cancer the mean total tumour volume was 5.83 ml (Fig. 4). Despite the greater tumour volume in stage A2, there was considerable overlap in the total volume of cancer in stages A1 and A2. Of patients with Stage A2 cancer, 24 (83%) had TZ cancer and 27 (93%) had PZ cancer. The mean volume of TZ cancer was 3.30 ml (range 0–13.86) and of PZ cancer was 2.53 ml (range 0–19.22) (Fig. 5A). Thus in patients with stage A2 disease, an average of 43% (0–100%) of the cancer present in stage A2 was of PZ origin. The pattern of distribution of cancer between the TZ and PZ was somewhat different in stages A1 and A2 (Fig. 5C). Although the volume of PZ cancer in stage A1 was generally small, 6 (46%) of the 13 stage A1 patients had a greater volume of cancer in the PZ than in the TZ and 2 of these had PZ cancer only (1 with SVI) (Fig. 5C). In contrast, in all of the 22 stage A2 patients with both TZ and PZ cancer, the volume of TZ cancer was greater than that of PZ cancer even though some of the PZ cancers were quite large (>0.5 ml). There was a distinct subgroup of 5 stage A2 patients who had only PZ cancer of large volume in the prostate (Fig. 5C). All 5 of these had extracapsular extension and 4 had seminal vesicle invasion as well. Thus the stage A2 group included some patients with large PZ cancers sampled at TURP and most of the Stage A2 patients with large TZ cancers, some of which were also associated with PZ cancers of considerable volume (Fig. 5C). The finding of PZ cancer in the TURP specimen, either alone or in combination with TZ cancer, occurred with comparable frequency in stage A1 (3 of 13) and stage A2 (6 of 29). Among the 9 patients with PZ cancer in the TURP specimen, 5 (56%) had ECE and 5 (56%) had SVI. Of the 33 patients with only TZ cancer in the TURP specimen, only 6 (18%) had ECE and none had SVI (Table 1).

Table 1 Correlation between Zone of Origin of Cancer in the TURP Specimen and Extraprostatic Spread in stage A Patients

Zone of origin	No. of patients	Pathology	
		ECE* No. (%)	SVI† No. (%)
TZ	33	6 (18)	—
PZ (± TZ)	9	5 (56)	5 (56)
Total	42	11 (28)	5 (13)

* $P < 0.03$, *t* test.

† $P < 0.001$, *t* test.

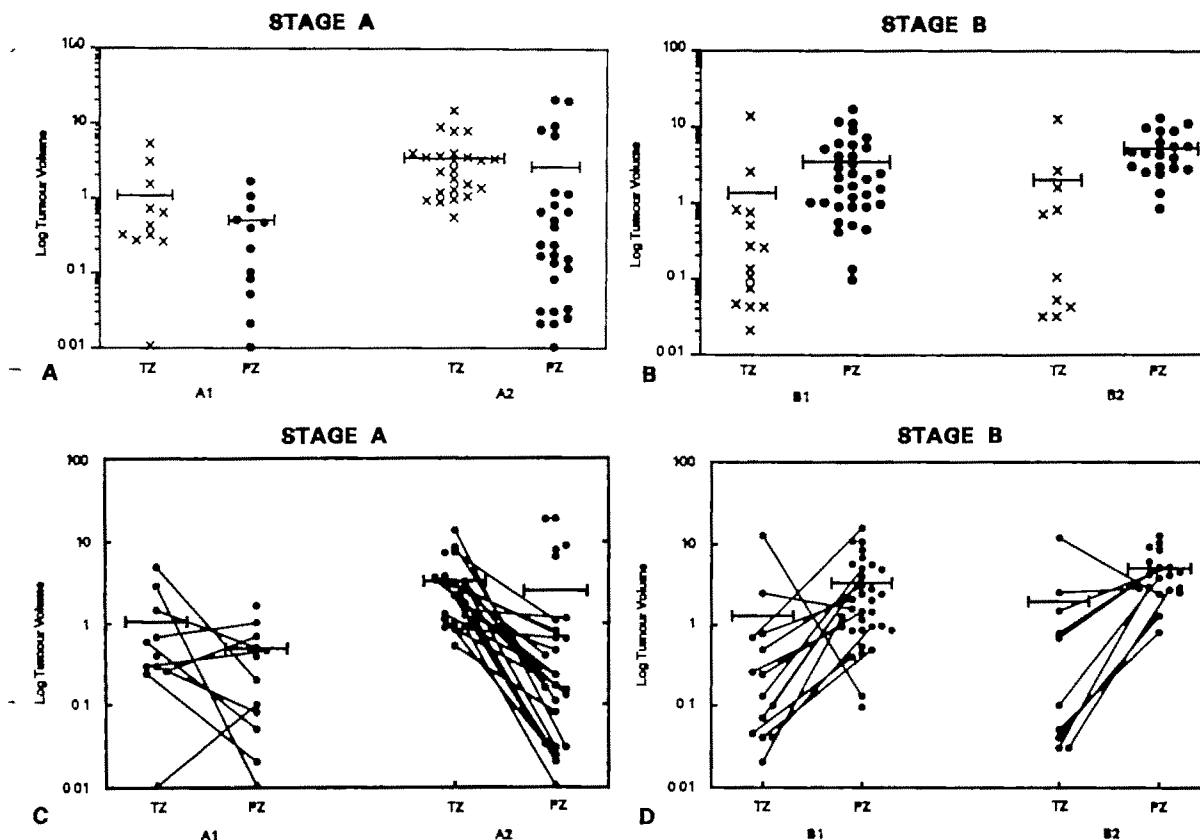


Fig. 5 Tumour volume by zone of origin (TZ = transition zone, PZ = peripheral zone origin) is shown for substages (A) A1 and A2, and (B) B1 and B2. Mean values are represented by crossbars. In stage A1, mean TZ tumour volume was 1.08 ml, in A2 3.30, in B1 0.55 and in B2 0.89 ml. Mean PZ tumour volume in stage A1 was 0.43 ml, in A2 2.53, in B1 3.30 and in B2 5.13 ml. In (C) and (D) the cancer volume in each zone is connected by a line for each individual case in which a separate cancer was present in both zones. Data points without cross lines represent patients with cancer in only one zone. Note the contrasting pattern in stage A (C), where the TZ cancer was generally much larger than the PZ cancer, versus stage B (D) where the opposite was generally true.

In patients with stage A1 and A2 cancer, the grade of PZ cancer was significantly higher than the grade of TZ cancer in the same gland ($P < 0.01$, Wilcoxon signed ranks test) (Table 2). However, there was no significant difference between the grade of PZ cancer in stage A1 and A2 patients or between the grade of TZ cancers in these same patients. Figure 6A shows the primary Gleason grade of each cancer plotted by log of tumour volume in each zone for each substage. TZ cancers were almost always well differentiated regardless of volume, while PZ cancers tended to be of higher grade with increasing volume.

Stage B

The mean total tumour volume in stage B1 patients was 3.86 ml (range 0.1–16.88) (Fig. 4). Fourteen (41%) of these patients had TZ cancer and all 34 had PZ cancer. The mean volume of TZ cancer

was 0.55 ml (range 0–13.0) and the mean volume of PZ cancer was 3.3 ml (range 0.1–16.18) (Fig. 5B). Thus TZ cancer comprised an average 8% (range 0–99) of the total volume of cancer in stage B1 and PZ cancer comprised 92% (range 1–100%). This pattern was similar in stage B2 patients, although the volume of cancer was greater, 6.02 ml (range 0.86–14.54) (Fig. 4). In stage B2 patients the mean volume of TZ cancer was 0.89 ml (range 0–12.1) and comprised 10% (range 0–83) of the total volume of cancer, while the mean volume of PZ cancer was 5.13 ml (range 0.81–12.91) or 90% (range 17–100) of the total volume of cancer in stage B2 patients (Fig. 5B).

The predominant cancer in the stage B patients was cancer of PZ origin (Fig. 5D). PZ cancer was present in every case and, when TZ cancer was also present (24 patients), the PZ cancer was larger in 88%. In only 3 patients was the TZ cancer larger

than the PZ cancer in the same gland, a pattern more typical of stage A. One such patient with stage B1 cancer initially presented with an elevated serum prostate specific antigen level. His large TZ cancer extended into the PZ and produced a subtle abnormality on digital rectal examination. The small (0.2 ml) PZ cancer present was an incidental finding. In stage B, PZ cancer was often present alone (57% of patients), with no associated TZ cancer. When TZ cancer was present it was usually "incidental", *i.e.* small volume and well differentiated (Table 2, Fig. 6B). With stage B, as with stage A, TZ cancer tended to be well differentiated even at large volumes, while PZ cancer was frequently moderately or poorly differentiated even at small volumes.

Discussion

The staging system for prostate cancer developed by Whitmore (1956), and later modified by Jewett (1975), represents an attempt to estimate the pathological extent of prostate cancer by clinical means. While useful for suggesting prognosis and for assigning appropriate therapy, this staging system also has several limitations (Scardino *et al.*, 1989). A difficulty arises in separating incidentally found "latent" cancers from "clinically important" cancers in the TURP specimen (Scardino, 1989). Several attempts have been made to use the features of cancer in the TURP specimen as a basis for prognosis (Bauer *et al.*, 1960; Correa *et al.*, 1974; Jewett, 1975; Boxer, 1977; Golimbu *et al.*, 1978; Cantrell *et al.*, 1981; Blute *et al.*, 1986; Epstein *et al.*, 1986), but neither the volume nor the percentage of cancer in the TURP specimen predicts the features of residual cancer in the gland in the individual patient (Epstein *et al.*, 1988; Neerhut *et al.*, 1988; Greene *et al.*, 1991a). In a proportion of patients with stage A1 prostate cancer, however defined, the disease eventually progresses (Blute *et al.*, 1986; Epstein *et al.*, 1986).

The description of histologically distinct zones within the prostate has provided the basis for a more logical analysis of prostate cancer (McNeal, 1978, 1981; McNeal *et al.*, 1988b). When stage A1 cancer is separated into that of TZ and PZ origin (Fig. 5A), it seems apparent that some of these cancers are incidental in nature with only small foci of TZ and PZ cancer present (Fig. 5C). These cancers, while histologically recognisable, may not have undergone all of the necessary genetic events to express full malignant behaviour (Carter *et al.*, 1990) and may never progress in the patient's

lifetime. Most cancers sampled by TURP (stage A) are TZ cancers (McNeal *et al.*, 1988b; Greene *et al.*, 1991a) but 90% of our stage A patients had a PZ cancer, which was, volume for volume, higher grade and more likely to extend outside the prostate than the TZ cancer initially detected (Greene *et al.*, 1991b).

The pattern of distribution of cancer in stages A and B was quite distinct (Figs 5C and D). Generally, stage A patients had larger volume TZ cancer than PZ cancer, while the reverse was true for stage B. There were, however, notable exceptions to this rule. Nearly half of our stage A1 patients had PZ cancer which was larger than the TZ cancer, and some patients had PZ cancer alone, a pattern seen in 17% of stage A2 patients as well. In stage A1 patients, these PZ cancers were generally small (all <1.7 ml) but were responsible for the occasional but surprising instance of ECE and of SVI seen in these patients with the earliest stage of clinically detected prostate cancer. PZ cancer was sometimes found without TZ cancer in stage A2 patients because the PZ cancer, though not palpable prior to TURP, was large enough to invade the TZ and be included in the TURP specimen. These cancers were particularly virulent, with all 5 patients having ECE and 4 having SVI. The finding of PZ cancer (or high grade tumour) in the TURP specimen should probably lead to a classification of the cancer as stage A2 regardless of the volume of tumour sampled. In the present series, 56% of patients with PZ cancer in the TURP specimen had ECE, and 56% had SVI. The only stage A1 patient with SVI had 0.4 ml (2.7%) of PZ cancer, Gleason grade 2 plus 3, in the TURP specimen.

While it was not uncommon for a PZ cancer to extend anteriorly and be sampled at TURP (stage A), it was rare for a TZ cancer to extend posteriorly to become the palpable (or "index") cancer in stage B. We found only one such example (Fig. 5D) in a patient who also had a separate PZ cancer of small volume. In stage A the incidental discovery of a TZ cancer acts as a marker for the presence of a PZ cancer, which may be larger and is usually less well differentiated and more likely to extend outside the prostate than the "index" TZ cancer. On the other hand, in patients with stage B disease, a PZ cancer was invariably present and only 43% had a TZ cancer which comprised only 9% of the total tumour volume on average. TZ cancer was consistently lower in grade than PZ cancer in the same gland (Table 2, Fig. 6) (Greene *et al.*, 1991b).

Because of their unique features, PZ cancers may be responsible for most instances of progression of

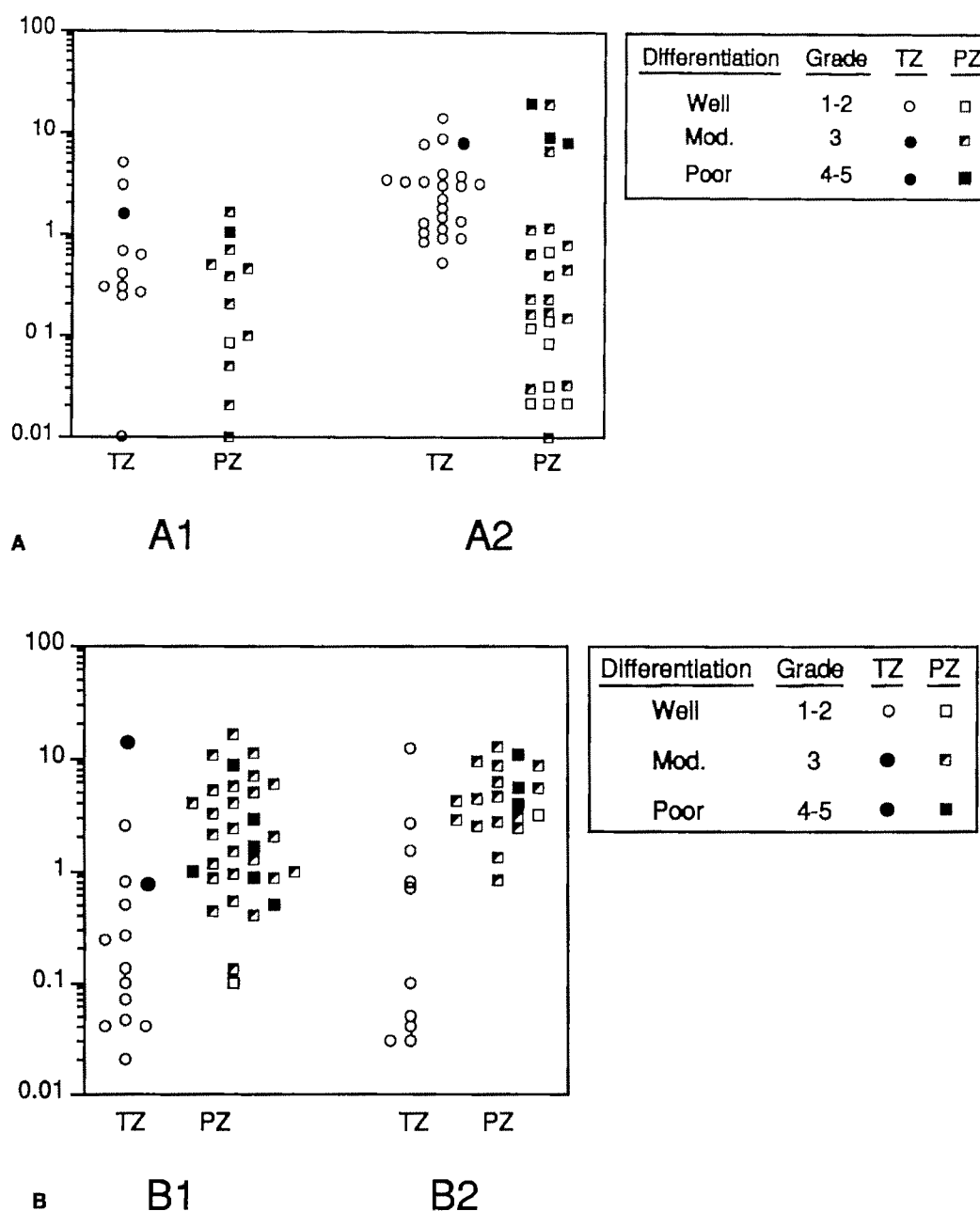


Fig. 6 Relationship of grade and tumour volume, by zone of origin, for (A) stages A1 and A2, and (B) stages B1 and B2. Each tumour was assigned a primary Gleason grade. Grades 1-2 represent well differentiated, 3 moderately differentiated and 4-5 poorly differentiated cancer. In cases where more than one primary Gleason grade was present in multifocal cancer in either zone, the highest grade was assigned to the cancer in that zone. Note the different pattern of tumour volume and differentiation between TZ and PZ cancers in both stage A and B tumours. Transition zone cancer is usually well differentiated even at large volume, while PZ cancer is often moderately or poorly differentiated even at low volume.

Table 2 Comparison between Median Grade (Gleason sum) and Range of Transition Zone (TZ) Cancers and Peripheral Zone (PZ) Cancers in each Substage.

Clinical stage	No. of patients	Gleason sum (range)		Wilcoxon signed ranks test <i>P</i>
		TZ	PZ	
A1	10	5 (2-6)	6 (5-7)	<0.01
A2	22	5 (4-6)	6 (5-7)	<0.01
B1	14	5 (3-5)	7 (5-7)	<0.01
B2	10	5 (3-7)	7 (5-8)	<0.01

Only prostates containing at least one TZ and one PZ cancer are included. In each substage the PZ cancers were significantly higher in grade than the TZ cancers, regardless of tumour volume (Wilcoxon signed ranks test).

the disease in stages A1, B1 and B2 prostate cancer. In stage A2, however, TZ cancers were generally larger than in other stages. Though generally well differentiated, these cancers may extend outside the prostate or metastasise. Indeed, we found ECE in 21% of the TZ cancers in stage A2. In addition, the stage A2 category includes PZ cancers comparable in volume to those in stage B1 (2.53 versus 3.36 ml). It seems reasonable, therefore, that progression of stage A2 cancer may stem from either the TZ or the PZ cancer. The higher rate of pelvic lymph node metastases in stage A2 is consistent with this hypothesis.

Studies of the zonal distribution of early stage prostate cancer have helped to clarify the relationship of clinical stage to pathological features and to prognosis of patients. Long-term clinical follow-up is necessary to substantiate this concept further. Knowledge of the zonal distribution helps to explain the rather modest correlation of tumour volume and grade in prostate cancer (Partin *et al.*, 1989). As we have previously shown, there is a markedly different volume/grade relationship for PZ and TZ cancers (Greene *et al.*, 1991b). TZ cancer is usually well differentiated even at large volume, while PZ cancer is usually moderately or poorly differentiated even at low volume. Furthermore, PZ cancer is more frequently associated with extraprostatic spread.

Patients with stage A1 cancer who have only a TZ cancer in the TURP specimen, a low PSA level and no evidence of PZ cancer on transrectal ultrasound (TRUS), probably have "latent" cancer that is unlikely to progress. In stage B disease, TZ cancer does not contribute substantially to total tumour volume and does not appear to contribute to the clinical course of the disease.

Even in stage A2, which selects the largest TZ cancers, PZ cancer plays a significant role and is more frequently associated with ECE and appears to account for all cases of SVI. Patients with stage

A2 cancer may have a poor prognosis because the volume of PZ cancer is comparable to that in stage B1 and there is often a large-volume TZ cancer as well. PZ cancer is associated with more unfavourable pathological features, and therefore could be expected to have a worse prognosis than TZ cancer.

The presence of PZ cancer in the TURP specimen, regardless of volume, suggests an aggressive cancer that requires treatment. We believe that it is the cancer in the PZ which is likely to be responsible for progression in patients with stage A1 prostate cancer. Therefore, evaluation of patients with focal, well differentiated cancer found in a TURP specimen (stage A1) should be directed at the peripheral zone, with digital rectal examination, transrectal ultrasound and prostate specific antigen, to detect residual PZ cancer, rather than at the transition zone with repeat TURP that is only likely to detect residual TZ cancer (Greene *et al.*, 1991b). We are following our stage A1 patients in an effort to validate this approach (Greene *et al.*, 1991a).

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Unusual Foreign Bodies in the Urethra and Bladder

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Summary—We report 8 cases of self-inserted unusual foreign bodies in the lower urinary tract, all being treated from 1976 to 1990. Three of them were located in the urethra and 5 in the bladder. Several objects were found (electric cable, tweezers, hairpin, drawing pin, pebbles, paper clip). In 4 cases the objects were inserted for masturbatory purposes. Five of the patients were psychologically ill or handicapped. The most common reason for consultation was dysuria, and the treatment procedures were endoscopy in 5 patients and cystotomy in the other 3.

Many cases of self-introduction of foreign bodies into the urethra and the bladder have been reported (Lackey and Acosta, 1973; Frozanpour, 1975; Desai and Brown, 1977; Wenderoth and Jonas, 1980; Villani and Leoni, 1983; Adams and Hudson, 1986; Kenney, 1988; Schnall *et al.*, 1989; Vigués *et al.*, 1989). Different items have been found (light bulb, fruit kernels, screws, pebbles, wire, etc.). The age of the patients ranged from teenagers to people in their eighties. Most cases were associated with mental illness, senility, psychiatric abnormalities or for sexual purposes.

The diagnostic methods and treatments performed were various and sometimes extreme. We report a well documented series of 8 cases of self-insertion of foreign bodies, the largest published in the literature we reviewed.

Patients and Methods

Between 1976 and 1990, 8 cases of foreign bodies in the lower urinary tract were treated. Seven of the patients were males, with ages ranging from 15 to 75 years (mean = 42.5 years). The objects were unusual (electric cable, plastic tubes, pebbles, wire, hairpin, paper clip, etc.) (Figs 1–3). Three of them were situated in the urethra and 5 in the bladder (Table 1).

Symptoms were acute, appearing shortly after

the introduction of the object in the case of patients with intra-urethral bodies; symptoms produced by the objects in the bladder were subacute, starting within 4 hours to 2 months after insertion. Three patients showed an evident oligophrenia, 2 of them suffered from psychiatric disorder, and the other 3 were psychologically normal (Table 2).

Diagnosis was based on a complete interview, clinical features, X-ray (that showed the radio-



Fig. 1 Case 1: electric cable in 15-year-old male; introduced for masturbatory purpose.



Fig. 2 Case 3: wire in the bladder in oligophrenic 15-year-old male with hypogonadotropic hypogonadism.



Fig. 3 Case 7: tweezers, hairpin and drawing pin; oligophrenic 41-year-old male.

opaque bodies) (Figs 1–3) and retrograde urethrography, performed when the foreign bodies were radiolucent. Five of them were removed by endoscopy, and cystotomy was carried out in the other 3 cases (Table 3).

Discussion

A review of the urological literature reveals the variety of self-inserted foreign bodies in the lower

urinary tract in both males and females. The aim of most of these reports has mainly been to show the urological manipulation performed in order to remove these objects (Schnall *et al.*, 1989; Vigués *et al.*, 1989), or to emphasise the unusual nature of the inserted bodies: light bulb (Wenderoth and Jonas, 1980), multiplicity of objects in the same

Table 1 Patient Data

Patient no.	Sex	Age	Foreign body	Location
1	Male	15	Electric cable	Urethra–bladder
2	Male	65	Plastic tube	Bladder
3	Male	15	Wire	Bladder
4	Female	17	Pebbles	Bladder
5	Male	64	Plastic tube	Bladder
6	Male	75	Urethral dilatator	Bladder
7	Male	41	Tweezers, hairpin and drawing pin	Urethra
8	Male	48	Paper clip	Urethra

Table 2 Clinical Data

Patient no.	Evolution	Clinical features	Objectives	Psychological profile
1	4 hours	Pain, tenesmus	Masturbatory	Normal
2	12 hours	Dysuria, haematuria	Masturbatory	Normal
3	2 months	Haematuria	Unknown	Oligophrenic
4	2 months	Cystitis	Unknown	Depression
5	6 days	Dysuria	Masturbatory	Normal
6	3 weeks	Dysuria, haematuria	Masturbatory	Dementia
7	12 hours	Dysuria	Unknown	Oligophrenic
8	3 days	Dysuria, haematuria	Unknown	Oligophrenic

Table 3 Diagnosis and Treatment

Patient no.	Location	Diagnosis	Treatment
1	Urethra-bladder	Clinical features, X-ray	Cystotomy
2	Bladder	Clinical features, X-ray	Cystotomy
3	Bladder	X-ray	Cystotomy
4	Bladder	X-ray, pebbles analysis	Endoscopy
5	Bladder	Clinical features, X-ray	Endoscopy
6	Bladder	Clinical features, X-ray	Endoscopy
7	Urethra	X-ray, urethrogram	Endoscopy
8	Urethra	X-ray, urethrogram	Endoscopy

patient (Desai and Brown, 1977) and wire (Lackey and Acosta, 1973). A psychiatric examination of young people with a history of urethral self-insertion has been reported recently (Kenney, 1988).

In the cases reported here the objects, which were similar to those described in the other reports, were removed by conventional procedures (endoscopy and cystotomy). It is notable that 5/8 patients were oligophrenics or had psychiatric problems; the only woman in the group was under antidepressive treatment. In the other 3 cases the purpose of insertion was clearly masturbatory, because the follow-up showed no relapse and no evidence of psychological abnormalities. The presence of foreign bodies in the lower urinary tract is easily suspected on the basis of the early symptoms, especially where they are in the urethra. The objects are mainly extracted by endoscopy (Villani and Leoni, 1983; Schnall *et al.*, 1989; Vigués *et al.*, 1989) or by cystotomy when the size and the shape of the foreign body make this procedure necessary. Conducting a psychiatric examination in every case of self-inserted foreign body (Kenny, 1988) is controversial, because most such patients are psychologically normal (Frozanpour, 1975; Wenderoth and Jonas, 1980; Villani and Leoni, 1983; Schnall *et al.*, 1989; Vigués *et al.*, 1989).

On the other hand, this examination is mandatory in patients with behavioural irregularities in order to detect psychopathy, relapses, or a very low level of intelligence.

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Surgical Technique for Inguinal Surgery and its Effect on Fertility in the Wistar Rat Model

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Summary—This study has explored the relatively neglected effects of operative manipulation of the vas deferens on fertility. Following unilateral vasectomy the contralateral vasa of 52 4-week-old Wistar rats were subjected to 7 different manipulations. After 7 weeks a fertility trial was conducted. All sham operated rats ($n = 18$) were fertile. Of the remaining 34 rats, 22 (65%) were sterile. All of those with tight ring reconstruction ($n = 6$) were sterile, due initially to venous obstruction. Nine of 14 rats with acute clip trauma (65%) remained fertile but 11 of 14 (78%) with full mobilisation were sterile owing to extensive avascular fibrosis of the vas deferens. These results suggest that over-zealous cord handling and operative technique in the immature animal is counterproductive and leads to vasal occlusion. This may have important repercussions in paediatric inguinal surgery, with a subsequent higher incidence of azoospermia and male subfertility.

The male contribution is significant for 25% of couples attending infertility clinics (Hull *et al.*, 1985). The outlook for the severely oligozoospermic and the azoospermic male is very poor. One preventable cause of obstructive azoospermia and male subfertility may be surgical damage to the vas deferens from operative handling of the spermatic cord during such procedures as childhood herniotomy, orchiopexy, hydrocele repair and, in the younger man, inguinal herniorrhaphy. Even in unilateral surgery, suboptimal contralateral vasa and testicular function may be further exacerbated by inadvertent damage to the healthy vasa and testis. Previous studies (Janik and Shandling, 1982) have examined histological changes in the vas deferens induced by cord handling, but fertility trials in such cases have not been performed. A Wistar rat model has been developed (Fig. 1) in order to determine what effect, if any, handling of the spermatic cord and in particular the vas deferens has on subsequent fertility.



Fig. 1 X-ray of Wistar rat model demonstrating right vasogram with a patent vas deferens, bladder full of contrast and incidental bilateral retrograde pyelograms.

Materials and Methods

A total of 52 sexually immature, random bred male Wistar rats aged 4 weeks (weight 74–115 g) were divided into 8 groups and underwent different operative manipulations (Table 1). Apart from Group 1 (the unoperated controls), all rats underwent a vasectomy on the left side and a different operative manipulation on the right side. Groups 2 (sham) and 3 (cord mobilisation) had minimal handling of the cord. In Group 4 the artery to the vas deferens was stripped by sharp and blunt dissection. In Group 5 the vas deferens was crushed by means of an arterial clip for 30 s. A tight herniorrhaphy repair was simulated by a constricting ring reconstruction over a 2-mm diameter pin in Group 6. A looser repair over a 4 mm pin was done in association with stripping the vas and crush injury in Groups 7 and 8 respectively. All operations were performed under full aseptic technique using intraperitoneal neuroleptanalgesia.

The male rats were then caged separately and allowed to mature for a further 7 weeks. At the age of 11 weeks each male rat was caged with 5 female Wistar rats. This fertility trial lasted for 3 weeks, during which the females had at least 3 oestrus cycles. The presence of vaginal plugs confirmed mating. At the completion of the fertility trial the rats were sacrificed. The presence of pregnancy, litter size and any fetal abnormality were recorded. The weight of each testis was recorded and histological assessment of the vasa and the testis

was performed without knowledge of experimental groups.

Statistical analysis

Comparisons within a rat group were made by means of the paired *t* test, and those between rat groups using the 2-sample *t* test.

Results

Fertility

The fertility data are summarised in Table 2, giving a total sterility rate of 42%. The 18 rats in Groups 1 to 3 (no operation, sham procedure, mobilising the cord respectively) had minimal handling of the cord and all were fertile. In the remaining 5 groups, 22 of 34 rats (65%) were sterile (Table 3). In Group 4, stripping of the vasa resulted in a sterility rate of 71% (*n* = 5). Severe crush injury to the vas deferens in Group 5 produced a low sterility rate, with only 2 of 7 rats sterile. In Group 6 (tight repair) all 6 rats were sterile; testicular infarction occurred in 4 but the remaining 2 had histologically normal testes and vasa deferentia (Fig. 2A). In Group 7, stripping the vasa together with loose inguinal reconstruction was particularly destructive, with a sterility rate of 86% (*n* = 6). In contrast, crush injury and loose inguinal reconstruction in Group 8 resulted in a sterility rate of only 43%, with 3 of 7 rats sterile.

In Groups 4 to 8 the incidence of testicular infarction (*n* = 8) was 24%, but in 4 rats it was associated with an abnormal vas deferens. In the remaining 4 animals (12%), infarction was the sole cause of infertility and these were all related to Group 6, which underwent tight reconstruction of the ring (Table 3).

The histological pattern of damage to the vas deferens in this study (Figs 2A and B) appears uniformly over a long segment, which is the case seen with post-operative occlusion (unlike infection, which is likely to produce multiple vasal blocks).

Testis weight

The mean left testicular weight/100 g body weight (0.48 g; SD 0.09) (Table 2) was significantly higher than that of the right (operative manipulation) (0.42 g; SD 0.17) (*P* = 0.027). Comparing the fertile right testis with the sterile right testis showed the mean weight of the right testis to be less in the sterile group (0.35 g; SD 0.24) than in the fertile group (0.47 g; SD 0.06) and this was statistically significant (*P* < 0.01).

Table 1 Details of Operative Procedures

Group no.	No. of rats	Operative procedure on the right side
1	3	Nil
2	8	Sham operation
3	7	Mobilising the cord only
4	7	Strip blood vessel off the vas
5	7	Crush injury arterial clip 30 s
6	6	Tight repair inguinal ring over 2 mm diam. pin
7	7	Strip blood vessel + loose repair inguinal ring over 4 mm diam. pin
8	7	Crush injury arterial clip 30 s + loose repair inguinal ring over 4 mm diam. pin

Note: In Groups 2–8 vasectomy was performed on the left side.

Table 2 Summary of Fertility Data and Testicular Weights

<i>Group no.</i>	<i>No. of rats</i>	<i>No. fertile</i>	<i>Sterility rate (%)</i>	<i>Mean weight right testis</i>	<i>Mean weight left testis</i>
1 Control	3	3	0	0.45	0.48
2 Sham	8	8	0	0.49	0.48
3 Mobilise cord	7	7	0	0.48	0.46
4 Strip	7	2	71	0.48	0.46
5 Crush	7	5	28	0.45	0.48
6 Tight repair	6	0	100	0.22	0.43
7 Strip + loose repair	7	1	86	0.37	0.49
8 Crush + loose repair	7	4	43	0.40	0.53

Weights are expressed in g/100 g body weight.

Table 3 Reasons for Sterility in Groups 4–8

<i>Group no.</i>	<i>No. of rats</i>	<i>No. of rats sterile</i>	<i>Abnormal vas</i>	<i>Infarcted testis</i>
4 Strip	7	5	5	—
5 Crush	7	2	2	—
6 Tight ring	6	6†	—	4
7 Strip + loose repair	7	6	6	3*
8 Crush + loose repair	7	3†	2	1*

Operated rats (n = 34). Infertile rats (n = 22) (65%).

In 4 cases* both the vasa and testis were damaged and responsible for sterility. However, 3 rats† from Groups 6 and 8 were sterile despite normal vasa and testes on histology. (See text for details).

Discussion

Since 30 to 35% of paediatric surgical practice consists of operations on the inguinal region, it is important to know what effect inguinal surgery has on the structures of the spermatic cord, especially the vas deferens. The vas deferens is a dynamic

structure. Previous surgery, infection, trauma, and even amyloidosis have all been shown to disrupt the propulsive action of the vas deferens, leading to defective sperm transport, retrograde flow, oligozoospermia and infertility (Janik and Shandling, 1982). Inadvertent transection of the vas deferens has an obvious effect. Since azoospermia may occur

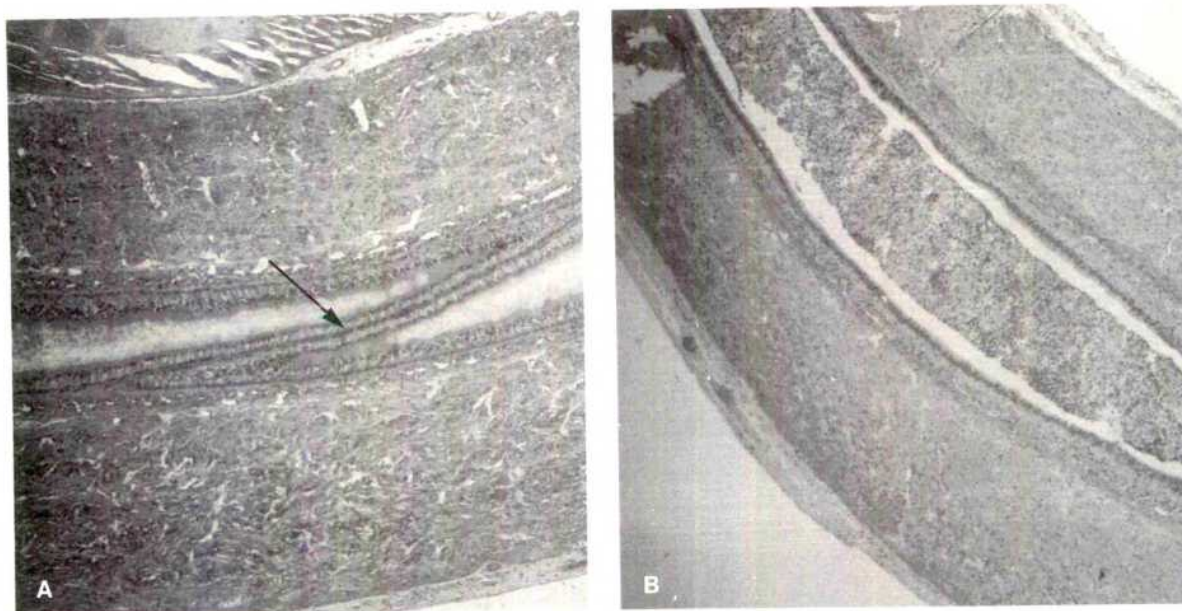


Fig. 2 (A) Normal rat vas deferens; epithelial spiral (arrow) with pseudocilia and sperm in lumen. (B) Abnormal rat vas deferens from inguinal region that had been stripped. There is loss of epithelial spiral, pseudocilia and absence of sperm with only cellular debris in the lumen.

after hernia repair despite normal testicular biopsy and vasography (Jequier, 1985), more subtle manipulations of the vas deferens may affect contractility and subsequent fertility.

Our results show that a variety of surgical techniques may significantly affect fertility. Tight ring construction and stripping the vasa are particularly destructive. Nine rats with acute clip trauma (65%) remained fertile but 11 (78%) with full mobilisation were sterile because of extensive fibrosis of the vas (Fig. 2B). Surprisingly, crush trauma over a short segment of the vas deferens did not always affect fertility.

Attention has previously been focused in animal studies on histological changes in the vas deferens (Janik and Shandling, 1982) and in the clinical context on obstructive azoospermia secondary to surgery, especially childhood herniotomy (Young, 1951; Hanley, 1955). Sparkman (1955) recorded an incidence of 1.6% following the inadvertent removal of a segment of the vas deferens with the hernia sac. Friberg and Fritjofsson (1979) investigated 76 men with sperm-agglutinating antibodies and found that 12 had undergone herniorrhaphy and were sterile. Ten were explored and 5 had vasal obstruction consistently in the area of previous surgery. Jequier (1985) described 9.8% of 102 patients with obstructive azoospermia following prior surgery or trauma. Five of these patients had

a unilateral herniotomy; only 2 of them had definite vasal obstruction on exploration; the other 3 had a patent vas deferens with a normal testis and yet were azoospermic. A similar incidence of azoospermia (13%) following inguinal herniotomy was reported by Petrovsky *et al.* (1985). The result of damage to the vas deferens and subsequent azoospermia will be obvious on semen analysis. The incidence of vas damage in unilateral herniotomy and inguinal surgery will be difficult to establish because of population movement, for the majority of the surgery is performed during childhood; masking by the contralateral side also creates problems.

Although the difficulties of extrapolating animal studies to man are acknowledged, in this study we have shown the vulnerability of the immature vas deferens. Vasectomy reversal in adults has a moderately high success rate (Linnet, 1983) and this may reflect the increased vulnerability of the immature vas deferens. Certainly in further adult Wistar rats we have found stripping of the vas to be less damaging (Sandhu and Osborn, in preparation).

Often with a unilateral lesion an assumption is made that the contralateral side is normal, but as testicular infarction or damage can occur, it is possible for an ischaemic testis to affect the contralateral side. Evidence from torsion experi-

ments in rats (Lewis-Jones *et al.*, 1987) suggests that sympathetic orchioepithia may lead to a rise in the naturally occurring serum cytotoxic antisperm antibody. It may cause a change in the specificity of this antibody, resulting in the production of an anti-testis antibody. This may be responsible for the contralateral impairment of sperm production in the absence of a cell mediated reaction (Wallace *et al.*, 1982). The present series supports on histological evidence the absence of allergic orchitis with a contralateral infarcted testis.

Antisperm antibodies following unilateral vasectomy alone may be relevant in inbred DBA/1J mice (Kessler *et al.*, 1985), which are known to be high antibody formers. Since the 15 Wistar rats (Groups 2 and 3) with unilateral vasectomy were all fertile, antisperm antibodies would not appear to be a significant problem in this study.

In summary, in the immature Wistar rat animal model the vas deferens and testis are vulnerable to operative handling, especially inguinal ring reconstruction and stripping of the cord. These results indicate the great care needed in handling the vas deferens during inguinal operations. In addition, although the vas deferens may be intact following surgery (even in unilateral cases), difficulties with sperm transport leading to obstructive azoospermia and male subfertility may be a long-term post-operative complication.

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Microsurgical Epididymovasostomy by Loop Intussusception

A New Technique in the Rat Model

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Summary—A new technique, epididymal loop intussusception into the vas deferens, is offered as an improved form compared with the side-to-end method. Loop intussusception has been experimentally studied bilaterally in 15 adult male rats. This report provides details of the technique. A 3-month anatomical and histological follow-up showed a 100% patency rate, no anastomotic stricture, and reabsorption of the blind intussuscepted loop in all but 3 cases. Macroscopic sperm granulomas were present in only 10% of the anastomoses examined. Advantages and disadvantages of microsurgical epididymovasostomy techniques are discussed.

In 1978, Silber made a major proposal for the treatment of obstructive azoospermia with the development of the microsurgical end-to-end epididymovasostomy of the single tubule to the vas. Nearly all subsequent experimental studies have been based on modifications of Silber's original technique (Ozdiler and Kelami, 1981; Belgrano *et al.*, 1983; Papadopoulos and Kelami, 1983). Despite experiments involving anatomically and physiologically normal adult rats, the anastomotic patency rates have remained persistently lower than 80%. In addition, there is the constant difficulty of deciding which epididymal stump after transection is the correct one for the anastomosis. Thus, despite the fact that the normal rat has relatively large genital organs and is quite well suited to experimentation, and despite the technically advanced microscopic equipment, no striking advance in experimental animal models has been made since Silber's original proposal.

In the clinical arena, many have begun to use a side-to-end microsurgical technique (Wagenknecht *et al.* 1980; Fogdestam and Fall, 1983; Lee, 1987; Thomas, 1987) in order to avoid the problem of

deciding which is the correct epididymal stump; however, no experimental data have shown a clear-cut advantage in patency rate, incidence of spermatic granuloma or other complications.

This new technique of loop intussusception was used in the experimental animal as a variation of the side-to-end technique; no decision was required regarding the correct transected epididymal end; there was less tissue trauma and no suture material within the epididymal lumen. The anatomical and histological results are presented and the technique of loop intussusception is described in detail.

Materials and Methods

A sterile technique, including iodine scrub solution, was used for 15 adult male Sprague-Dawley rats (average weight 500–600 g) undergoing bilateral microscopic epididymovasostomy. Pharmaceutical agents included Nembutal anaesthesia intraperitoneally (70 mg/kg body weight), gentamicin prophylaxis intramuscularly (4.4 mg/kg body weight) and saline solution for irrigation. Microsurgical instrumentation included bipolar coagulation, vasodilators, forceps, micro-scissors straight and curved, and needle holder. The suture material comprised

sterile 10/0 nylon on a 70 micron needle, 6/0 chromic and 6/0 nylon sutures. Light microscopy with 100 $\times$ magnification was used to evaluate the vas fluid.

Operative technique

A longitudinal scrotal midline incision is made and the scrotal contents delivered into the wound after dissecting the tunica off the testis (Figs 1A and B). The epididymis is then exposed via a short transverse incision between the tunical vessels, and under 16 $\times$ magnification of the microscope the epididymis is dissected from the lower testicular pole. The vas deferens is sharply separated from the surrounding tissue and the vascular bundle ligated with 10/0 nylon sutures. The vas deferens is transected (Figs 1C and D). A circular excision of the epididymal adventitia is made equal to the size and shape of the transected vas deferens. Any part of the epididymis can be delivered into the field with slight pressure applied to the epididymis. Sharp, delicate dissection under microscopic visualisation (16 $\times$ and/or 25 $\times$) is done of the single loop of the tubule (Fig. 1E): this is only done outside the loop so that the connective tissue

between the loop is spared for the placement of the 2 inner layer sutures.

In this experimental model with the full tubules of the anatomically normal rat, the loop is not opened before the placement of two 10/0 nylon sutures for the inner layer. (Note: there is no limitation to the technique if the loop is accidentally opened in the animal model or, for example, in clinical practice, where the loop must be opened in order to assess the presence or absence of sperm, as with the side-to-end technique). As a tacking manoeuvre in the outer layer, a 10/0 nylon suture is placed on the posterior aspect of the vas deferens and the outer epididymal tissue. (This is not only for support but is also a reference point for the placement of the 2 inner layer sutures (Fig. 2A)).

The suture of the inner layer is placed at 6 o'clock relative to the vas deferens from outside to inside through only the inner muscularis and then through the mucosa into the lumen. This suture is then placed through the connective tissue at the posterior aspect of the base of the loop *i.e.* not through any part of the tubule itself. This suture is then brought back parallel to the first pass in the vas but in the

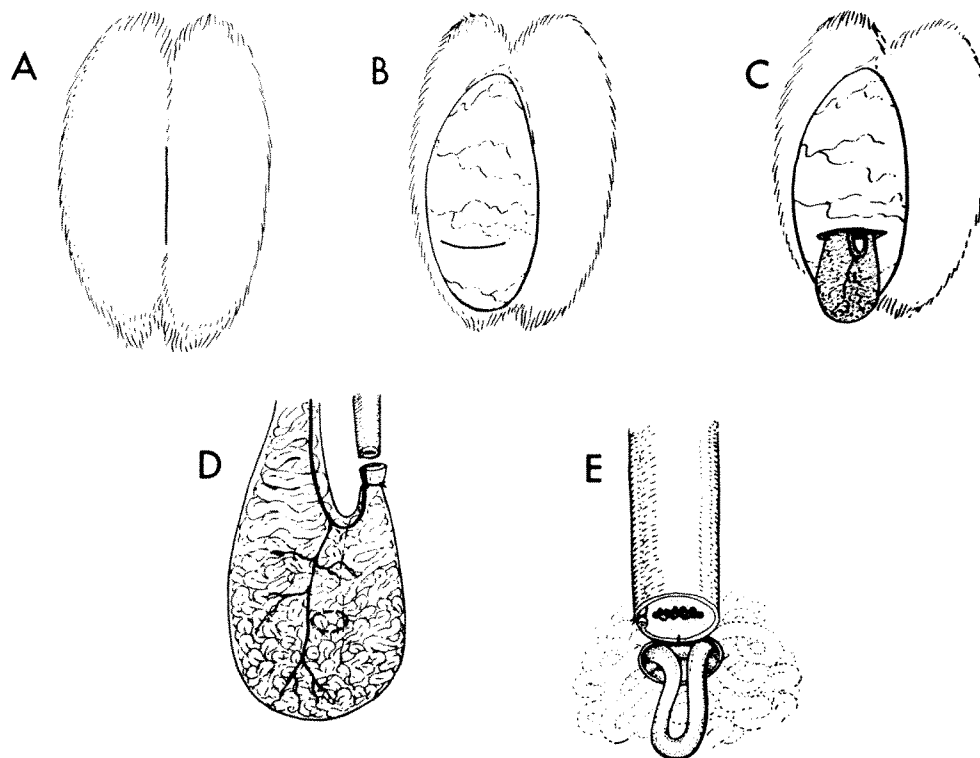


Fig. 1 Surgical approach for microsurgical epididymovasostomy in rats. (A) Midline longitudinal scrotal incision. (B) Transverse tunical incision. (C) Separation of epididymis and vas deferens from the testis. (D) Transection of vas deferens and proximal end ligation. (E) Single epididymal loop dissection. Fixation of vas deferens with a single suture to the opening on epididymis adventitia.

opposite direction. One then cuts off the needle, leaving tails of the suture long enough to prevent this first inner layer suture from pulling out (Figs 2A, and C, suture I).

The second suture is placed at 12 o'clock relative to the vas (or 180° relative to the first suture) through the entire vasal wall from outside to inside at a distance 3 times the width of the epididymal tubule. By previously positioned vasodilator the mucosal wall of the vas is protected from the needle, which is retrieved through the lumen of the vas. This needle is then passed through the apical connective tissue of the epididymal loop and on the anterior aspect (compared with the previous one on the posterior aspect and connective tissue on the base of the loop). Then the needle is passed through the vas deferens from the lumen to the outside, close to the initial pass but in the opposite direction. No suture touches the mucosa of the epididymal tubule (Figs 2A and C, suture II). Neither of these 2 sutures of the inner layer is tied at this point.

The genu of the loop is then excised tangentially

and thereby widely exposes the epididymal tubule lumen (Figs 2A and D). Each of the 2 previously placed sutures is then pulled in opposite directions, the first towards the epididymis and the second towards the vas. This allows the entire loop to slide into the lumen of the vas for a distance equal to 3 times the width of the transected tubule (Fig. 2D). The second suture is tied first, followed by the knot of the second, and the ends are cut quite short in order to minimise tissue reaction to foreign material (Figs 2B and E). The outer layer is closed using approximately 6 interrupted simple 10/0 nylon sutures in addition to the first tacking suture. These are between the epididymal adventitia and also the vasal adventitia and outer muscularis.

The same operation is performed on the contralateral side and the scrotal skin is closed with a continuous running suture of 6/0 chromic gut. Everything is then replaced through the tunical incision, which is closed with a continuous running suture of 6/0 chromic gut in 2 planes. The closed wound is painted with iodine solution. Neither

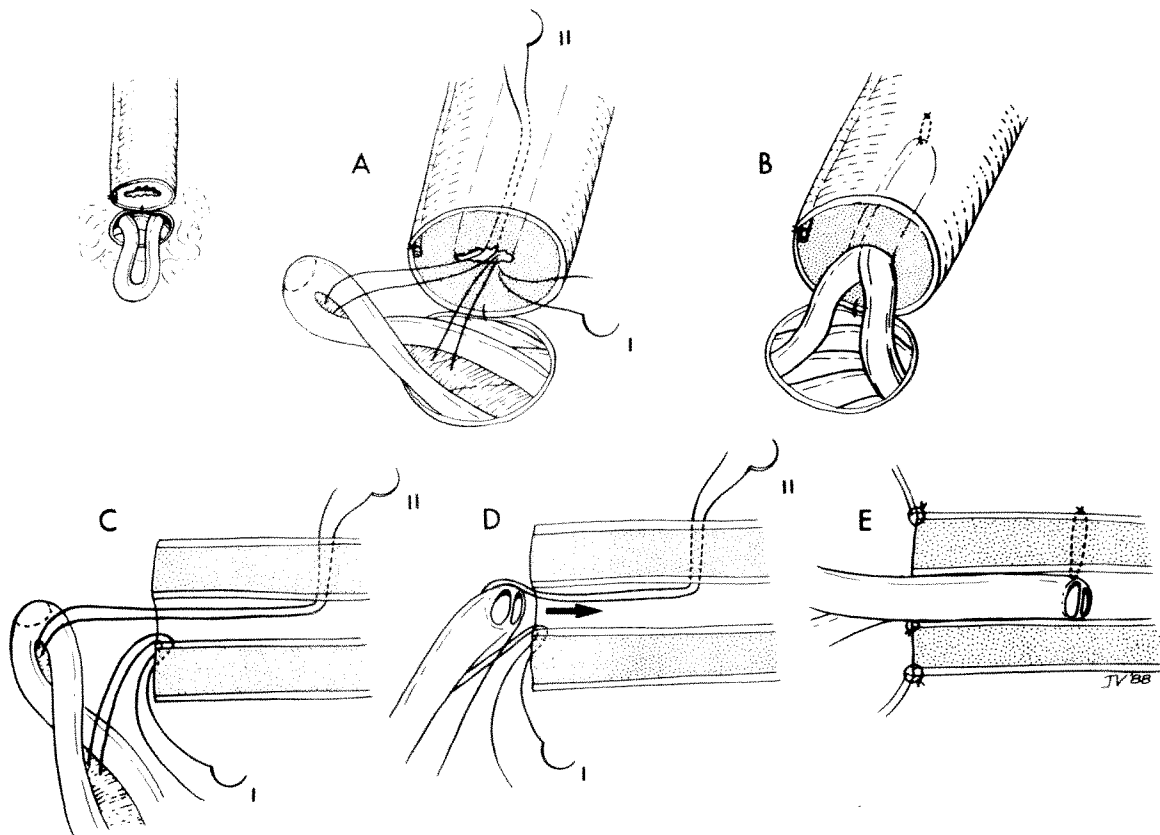


Fig. 2 Placement of sutures (I and II) for microsurgical epididymovasostomy by loop intussusception. Note that both sutures are outwith the lumen of the epididymal tubule.

drains, scrotal support nor dressings are used. The entire operation can be completed within 1½ h and only 1 injection of Nembutal intraperitoneally is required. All operations were performed by one surgeon (K.B.S.) Post-operative management of the rats included a clean cage with fresh bedding and towel and no limitation on food and water.

Post-operative evaluation

Under intraperitoneal Nembutal anaesthesia, the experimental animals were re-explored 3 months post-operatively through a low midline abdominal incision, *i.e.* different from the previous scrotal approach. The scrotal contents were delivered by pushing up the scrotum inferiorly and by picking up the testicular fat. All anastomoses were evaluated for the presence of scar tissue, infection, revascularisation of the epididymal tail, patency and the presence of spermatic granulomas. All rats were sacrificed after re-exploration and evaluation.

The patency rate was checked by microscopic visualisation under 16× magnification. Although the vasal wall is relatively thick, it is gelatinous and transparent, so that the sperm content can be recognised easily (Fig. 3). After transection of the vas, the epididymal tail was squeezed. If the lumen at the anastomotic site was completely open, sperm efflux was abundant; if obstructed, there was no

sperm in the vas and the epididymis was full of stagnated sperm. Under light microscopy the fluid of the vas was examined for the presence of sperm. Longitudinal sections of the fixed specimens were used for histological confirmation of patency in all 30 anastomoses.

The incidence of spermatic granulomas was determined from the fixed specimens of anastomosed epididymis and vas deferens. The method of fixation included placement of specimens at length but not under tension and storage in 10% formalin for at least 24 h. Longitudinal sections provided a record of the incidence of spermatic granulomas, even though they were very small, *e.g.* 2 mm. Without longitudinal sections of fixed specimens only large, externally apparent spermatic granulomas would be included. A record was made of those spermatic granulomas seen before histological evaluation ("macro") and after histological confirmation ("micro").

Results

There were no complications 3 months post-operatively—no infection, no anastomotic disruption and no scar tissue. All 30 anastomoses were revascularised and patent; 77% (23/30) had no evidence of spermatic granulomas, either macroscopically or microscopically; 10% (3/30) had macroscopical spermatic granulomas on the longitudinal sections. Despite the presence of these macroscopic spermatic granulomas (usually adjacent to an anastomosis), there was neither morphological nor histological evidence of anastomotic compression; 13% (4/30) had only microscopic evidence of spermatic extravasation. In 3 of 30 anastomoses, intussuscepted epididymal tubules were not completely absorbed 3 months later. In all others the reabsorption was complete and anastomotic sites healed perfectly (Fig. 4).

Discussion

The principal difficulties encountered with Silber's original end-to-end technique for epididymovasostomy are: (1) determining which end of the epididymis is proximal, *i.e.* there is a risk of connecting the distal end or blind loop to the vas deferens; (2) the end-to-end method requires transection and at times pressure on the epididymis; (3) a poor tubule match increases the risk of sperm leakage at the anastomotic site. Because of the difficulties encountered using Silber's method, many modifications have been proposed (Amelar

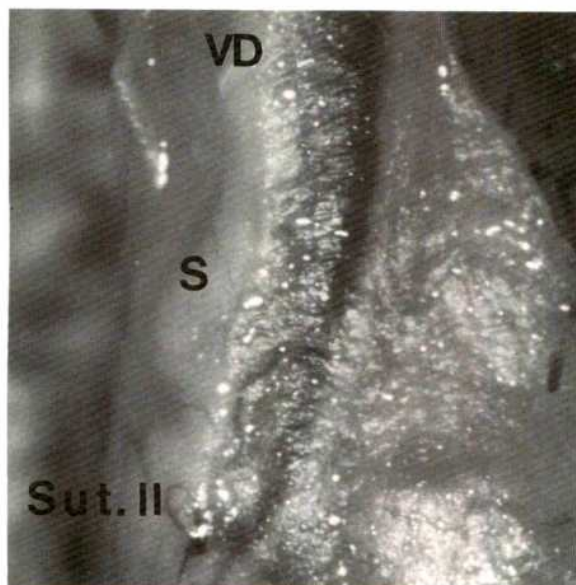


Fig. 3 Re-exploration of anastomosis 3 months post-operatively. Anastomosis patency is easily recognisable because of tissue transparency. VD = Vas deferens. S = Visible semen flow through vas deferens. Sut. II = 10/0 nylon suture for epididymal loop intussusception in vas deferens. (16× magnification).

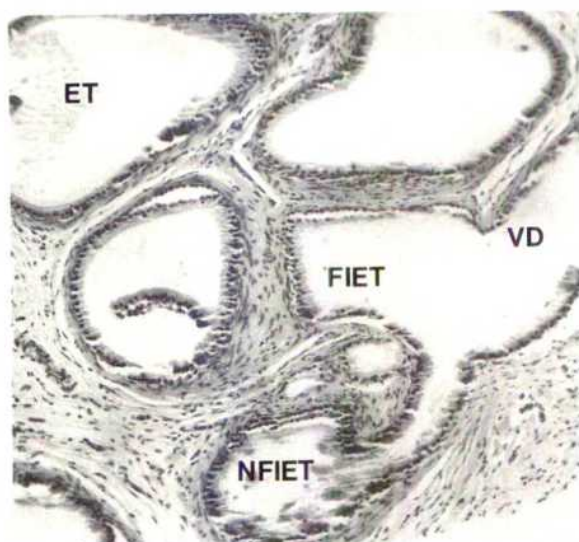


Fig. 4 Histological appearance 3 months post-operatively. Longitudinal section through anastomosis. ET = Epididymal tubule, cross section. FIET = functional (proximal) intussuscepted epididymal tubule. NFIET = Non-functional (distal) intussuscepted epididymal tubule. VD = Vas deferens. (H and E $\times 100$).

and Dubin, 1977; Belgrano *et al.*, 1983; Drawz *et al.*, 1985). The side-to-end technique has been promoted by Wagenknecht *et al.* (1980) as a superior method of reconnecting the epididymal tubule to the vas deferens. Subsequent clinical reports (McLaughlin, 1982; Wagenknecht, 1985; Fogdestam *et al.*, 1986; Thomas, 1987) and experimental studies (Vancaillie *et al.*, 1984; Drawz *et al.*, 1987) have supported his view. The side-to-end technique solves the 3 problems associated with the end-to-end anastomosis but it presents the surgeon with another difficulty—the accurate placement of inner layer sutures (McClure, personal communication). Incorrect placement can lead to sperm leakage, a blocked tubule, or stricture at the anastomotic site. Therefore, even under ideal experimental circumstances, both the end-to-end and the side-to-end techniques have an unduly high incidence of complications and a patency rate less than 80% (Ozdiler and Kelami, 1981; Belgrano *et al.*, 1983; Vancaillie *et al.*, 1984; Papadopoulos and Kelami, 1985). The side-in-end microsurgical epididymovasostomy by loop intussusception has all of the advantages of the side-to-end method. In addition, when the anastomosis is performed, the tangential incision on the genu opens the epididymal tubule very widely, and in the completed anastomosis there is no suture material in the lumen of the

epididymal tubule. Another benefit is that the distal non-functional epididymal stump serves as a biological method of tamponade, blocking sperm leakage. Our animal experiments indicate that the segment of non-functional epididymal stump located in the lumen of the vas deferens is usually resorbed over time (in 90% of anastomoses after 3 months). The epididymovasostomy by loop intussusception is especially suitable in the case of a very thin, fragile epididymal tubule, where end-to-end or side-to-end methods have a high incidence of failure, or in the situation of an obstruction in the head of the epididymis, where a bypass of the obstruction is indicated (Silber, 1980; Schoysman and Bedford, 1986).

This study has shown that the outer anastomotic layer is not responsible for spermatic granuloma formation. Prevention of sperm leakage is dependent on the quality of the inner layer closure, *i.e.* perfect mucosal to mucosal approximation with no tension. The presence, size and anatomical position of spermatic granulomas do not appear to affect the anastomotic patency rate. This explains the success of traditional epididymovasostomy techniques based on forming spermatic fistulae; however, spermatic granulomas produce local irritation and, more importantly, lower sperm viability by the induction of anti-sperm antibodies (Rumke and Hellings, 1959; Alexander *et al.*, 1974; Alexander and Schmidt, 1977).

In conclusion, clinical and experimental data show the superiority of side-to-end over end-to-end epididymovasostomy. The intussusception of an epididymal loop inside the lumen of the vas deferens provides a 100% patency rate with no anatomical or histological evidence of stricture, perfect healing with reabsorption of the intussuscepted blind loop in 27 of 30 anastomoses, and a reasonably low incidence of macroscopical spermatic granulomas (10%). There are no technical limitations for clinical practice. The technique requires only 2 stitches, does not depend on tubule size and does not require the determination of proximal and distal ends of the epididymal tubule.

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Animal Models for Epididymoepididymostomy. Development of an Alternative Microsurgical Procedure for Vasoepididymostomy

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Summary—The present success rate for high level microsurgical vasoepididymostomy in patients with obstructive azoospermia is generally poor in comparison with more distal vasoepididymal bypasses, suggesting that the development of a high level bypass method which preserves the distal maturation and storage functions of the epididymis might increase the fertility success rate. To achieve this we have developed a segmental bypass of the distal caput-proximal corpus regions of the epididymis (epididymoepididymostomy) using the rat and rabbit as animal models.

In this procedure the epididymides of 11 adult male Sprague-Dawley rats were exposed through a scrotal incision and a convolution of the duct in the proximal corpus region was attached to an opened convolution in the mid-caput epididymides using a standard microsurgical technique. Each male was rested for at least 3 months after the microsurgical bypass operation to allow the pre-operative sperm contents of the caudal storage region to be replaced by post-bypass spermatozoa. Six of the 11 rats were proven fertile after surgery by siring litters from mating trials up to 11 months later. The patency of anastomoses was confirmed in 3 animals by laparotomy and recovery of large numbers of sperm with normal motility from the cauda epididymidis distal to the anastomosis site and also from the vas. Similar unilateral surgery in 2 adult male rabbits resulted in normal post-operative semen profiles in 1 and an *in vivo* fertilisation rate of 100% from 1 mating trial 8 months after surgery.

The successful development of a reliable animal model for epididymoepididymostomy provides an experimental tool for studying the function of the epididymis. This technique may also have clinical application as an alternative to high level vasoepididymostomy in selected patients with obstructive azoospermia.

Various surgical procedures have been developed to correct obstructive azoospermia caused by epididymal blockage. Vasoepididymostomy using a side-to-side anastomosis to create a fistula had been the standard approach and was successful in many cases of post-inflammatory epididymal blockage (Jitendra and Phadke, 1975; Hendry, 1981). The development of a microsurgical end-to-end vasoepididymostomy technique in the last 15 years has produced an improvement in bypass results (Silber, 1978, 1980a and b, 1988; Silber *et al.*, 1988; Southwick and Temple-Smith, 1988). However, with few exceptions, the success rate in high level

epididymal blockages is often low, with many patients remaining infertile (Silber, 1978, 1980a; Schoysman and Bedford, 1980; Southwick and Temple-Smith, 1988). In many cases, although a technically successful high level microsurgical vasoepididymostomy was performed, sperm quality and quantity remained poor with a high percentage of immature forms. Such spermatozoa have presumably not undergone the normal maturation which occurs during their passage through the epididymis, suggesting that if normal epididymis distal to the site of obstruction could be used, the outcome of bypass surgery might be improved. Epididymoepididymostomy (E/E) was first described by Krylov and Borovikov (1984) as a corrective procedure for

localised epididymal blockage in infertile men. This technique involved the direct microanastomosis of a single proximal tubule to a single distal tubule in the epididymis and although some success in terms of post-operative semen production was reported, no pregnancies were obtained. With the exception of a preliminary report of the present study (Temple-Smith *et al.*, 1989), the potential of this technique has remained unexplored.

The aim in this study has been to develop reliable E/E microsurgical techniques in 2 species of laboratory animals and then to use these animal models as an experimental approach for studying the sperm maturation function of the epididymis. We now report the successful development of animal models for E/E.

Materials and Methods

The technique used was a basic segmental bypass of part of the distal caput region of the epididymis in the rat and rabbit. In 11 adult male Sprague-Dawley rats and 2 adult male New Zealand white rabbits, the epididymis was exposed through a scrotal incision after induction of anaesthesia with intraperitoneal (rats) or intravenous (rabbits) injection of sodium pentobarbitone (Nembutal 60 mg/ml). The epididymis was first divided between ligatures of 6/0 nylon in the proximal corpus region (Fig. 1A and B) and the region of the epididymis distal to these sutures was then mobilised (Fig. 1C) to allow a tension-free anastomosis.

In the rat, because of the extremely small

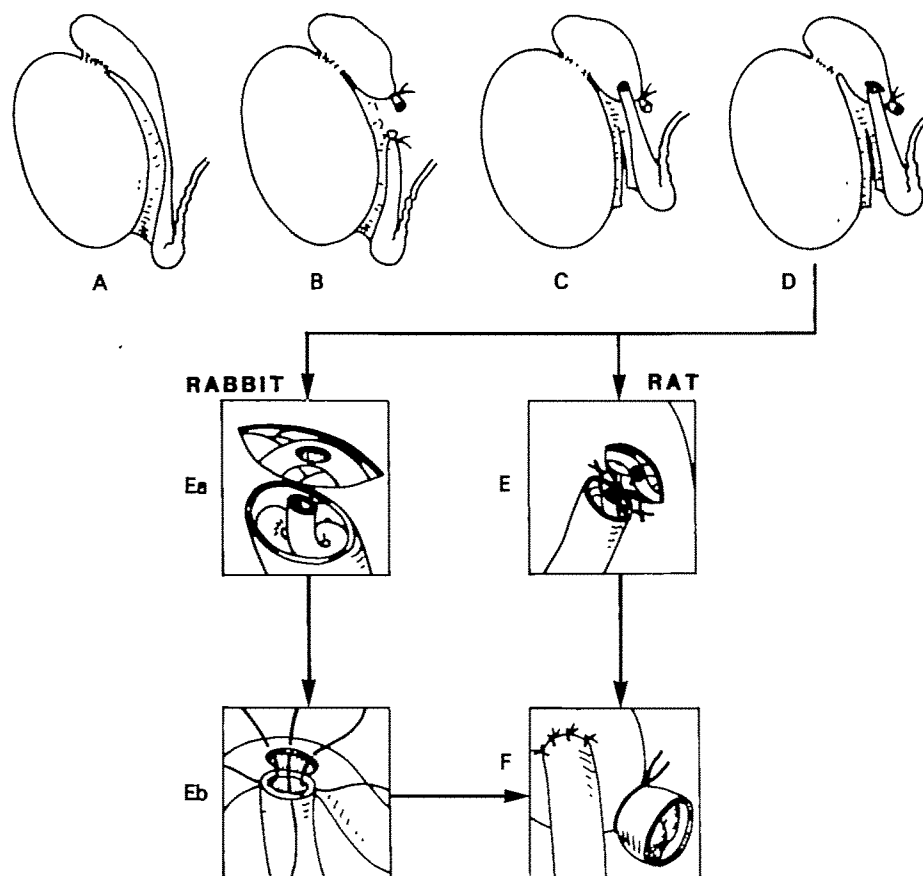


Fig. 1 Microsurgical procedure for epididymoepididymostomy in the rat and rabbit. (A) Normal relationships of testis and epididymis prior to surgery. (B) Ligation and epididymotomy at the junction between caput and corpus regions of the epididymis. (C) Mobilisation of the distal part of the epididymis by dividing the mesorchial membrane attaching testis and epididymis. (D) Apposition of the proximal corpus and distal caput anastomosis sites. (E) Rat—a surface convolution in the distal caput region has been deroofed and the corpus duct and associated adventitia sutured to the caput adventitia over the open caput duct using 10/0 nylon sutures. (Ea) Rabbit—a surface convolution has been exposed through an incision in the distal caput adventitia and deroofed, and the transected corpus duct aligned against it. (Eb) Rabbit—end-to-side microanastomosis showing position of three 10/0 sutures prior to closure of the inner layer. (F) Completed anastomosis showing alignment and closure of the adventitial layers.

diameter of the ductus epididymidis, exact end-to-end apposition of the severed ducts was difficult. Because of this the formation of a fistula was used as the standard approach with a 2-layer end-to-side anastomosis (Fig. 1). First the tunica vaginalis and adventitia overlying the distal caput epididymidis were incised (Fig. 1D) to expose a single convolution of the duct which was opened and the severed duct in the proximal corpus region was then sutured with interrupted 10/0 nylon sutures to the adventitia surrounding the deroofed tubule using standard microsurgical techniques (Southwick and Temple-Smith, 1988) (Fig. 1F). In the rabbit a more accurate anastomosis was possible because of the relatively larger size of proximal ducts (Fig. 1Ea) and direct suturing of mucosa to mucosa was possible using on average three 10/0 sutures (Fig. 1Eb). A second outer layer of 10/0 sutures was then placed in the tunica to support the anastomosis in all cases (Fig. 1F).

In the first 2 rat operations a side-to-side anastomosis was attempted but this was found to be technically more difficult than the end-to-side approach and was abandoned. The procedure was either carried out bilaterally or, if unilateral, the contralateral epididymis was obstructed to prevent spermatozoa from this side entering the ejaculate. The earlier operations were carried out unilaterally because of the length of time required to complete the procedure. The first unilateral operation took 3 h. As experience was gained, it was eventually possible to perform the procedure bilaterally in just under 2 h. All operations were carried out by the same surgeon.

Each male was left for at least 3 months after microsurgical bypass to allow clearance of pre-operative spermatozoa from the caudal storage region of the operated side and from the epididymis and vas on the contralateral side in those cases where the operation was not performed bilaterally. The fertility of the rats was tested by mating trials on 2 occasions over the next year. At the conclusion of the experiment, laparotomy was performed, photographs taken and sperm samples aspirated from the vas and sites in the epididymis proximal and distal to the anastomosis using a standard microaspiration technique (Southwick and Temple-Smith, 1988). The testis and the epididymis were then fixed in Bouin's solution and sent for histology using standard preparation techniques. Semen profiles in the rabbits were monitored by weekly collections of ejaculates using routine manual semen analysis procedures recommended for human semen analysis (Belsey *et al.*, 1980). Fertility was

tested in the successful rabbit by double mating to an oestrus female, which was given 100 I.U. human chorionic gonadotrophin immediately after mating, killed 36 h later and the oviducts flushed with Ringer's solution. Flushings were examined for unfertilised oocytes and embryos which were identified using phase contrast microscopy.

Results

Six of the 11 operated rats were proved fertile after surgery by siring litters from the first mating trial 4 months post-operatively (Table 1). At the second mating trial at 11 months, 4 of these 6 rats successfully sired litters. Laparotomies were performed on the 2 rats (nos. 4 and 6) which had failed to sire a second litter. The testes were found to be atrophic with sperm granulomata in the epididymis adjacent to the site of anastomosis. Laparotomies were performed on the other 5 rats which had failed both mating trials and findings were similar, suggesting that leakage at the anastomosis site with subsequent granuloma formation and testicular atrophy had probably been the cause of failure.

Two (nos 8 and 9) of the 4 rats which had 2 successful mating trials were examined by laparotomy 1 year after surgery. In rat no. 8 the unilateral anastomosis was found to be functioning with the ductus epididymidis containing large numbers of spermatozoa distal to the anastomosis, no proximal distension of the caput region and no granuloma formation. The testis was of normal size and consistency and subsequent light microscopy demonstrated normal spermatogenesis and confirmed the patency of the anastomosis with a histologically normal epididymis proximally and distally (Fig. 2). Semen samples aspirated microsurgically at the time of laparotomy showed large numbers of sperm in the cauda epididymidis and vas with progressively increasing motility and reduction in immature forms from caput through the cauda to the vas as indicated by reducing numbers of spermatozoa with cytoplasmic droplets still attached (Table 2). The second animal (no. 9) had had a bilateral operation. At laparotomy the right side was found to have failed with granuloma formation and testicular atrophy, but the left side had been successful. The findings were similar to those in rat no. 8. The testis was normal and the anastomosis was functional, as shown by the presence of large numbers of structurally mature, motile spermatozoa in fluid aspirated from various sites in the epididymis and vas. Histological examination of the testis and epididymis again showed normal sper-

Table 1 Results of Epididymoepididymostomy

Animal	Operation	Mating trials		Status of anastomosis at autopsy
		1st	2nd	
1	Unilateral*	Sterile	Sterile	Failed
2	Unilateral	Sterile	Sterile	Failed
3	Unilateral	Sterile	Sterile	Failed
4	Unilateral	Pregnancy (4 months)	Sterile	Failed
5	Unilateral	Sterile	Sterile	Failed
6	Unilateral	Pregnancy (5 months)	Sterile	Failed
7	Unilateral	Sterile	Sterile	Failed
8	Unilateral	Pregnancy (4 months)	Pregnancy (11 months)	Functional
9	Bilateral	Pregnancy (4 months)	Pregnancy (11 months)	Left functional. Right failed
10	Bilateral	Pregnancy (4 months)	Pregnancy (11 months)	Not available†
11	Bilateral	Pregnancy (4 months)	Not tested	‡

* Where bypass was unilateral, the contralateral epididymis was obstructed at the time of surgery.

† Animal died and scrotal content eaten by female.

‡ Not yet examined.

Periods in parenthesis indicate the time after operation at which mating trials were conducted.

matogenesis and confirmed an intact anastomosis and normal epididymis.

Of the 2 remaining rats, no. 11 is alive and awaiting further mating trials but no. 10 died of unknown causes 13 months after surgery. Unfortunately, when discovered the testes and epididymidis of this animal had been eaten by its mate and were therefore not available for examination.

Unilateral E/E was performed on 2 rabbits. In the first, sperm counts rapidly fell to zero post-operatively and at laparotomy the anastomosis was found to have failed. In the second, post-operative semen profiles quickly returned to normal (Fig. 3). A mating trial performed 8 months after surgery showed an *in vivo* fertilisation rate of 100%.

Discussion

This study demonstrates that, with experience, E/E surgery can be performed successfully in 2 different laboratory animal species and the results suggest that experimental E/E procedures may be useful in future to define the regional importance of the epididymis in sperm maturation. Comparison of the earlier failures with the last 4 successful operations demonstrates the learning curve seen in the development of any new microsurgical procedure. The small size of the ductus epididymidis in the rat and rabbit presents a challenge to the operator greater than the anastomoses of the small vessels under the microscope and, unlike vasoepi-

Table 2 Changes in Motility (%) and Cytoplasmic Droplet Retention (%) in Sperm Samples Collected above (caput) and below (cauda, vas) Functioning Epididymoepididymal Bypasses

Animal no.	Site of collection	% Motility	% Cytoplasmic droplets
8	Caput epididymidis	26	44
	Cauda epididymidis	58	12
	Vas	70	<5
9	Caput epididymidis	—	71
	Cauda epididymidis	37	38
	Vas	47	24

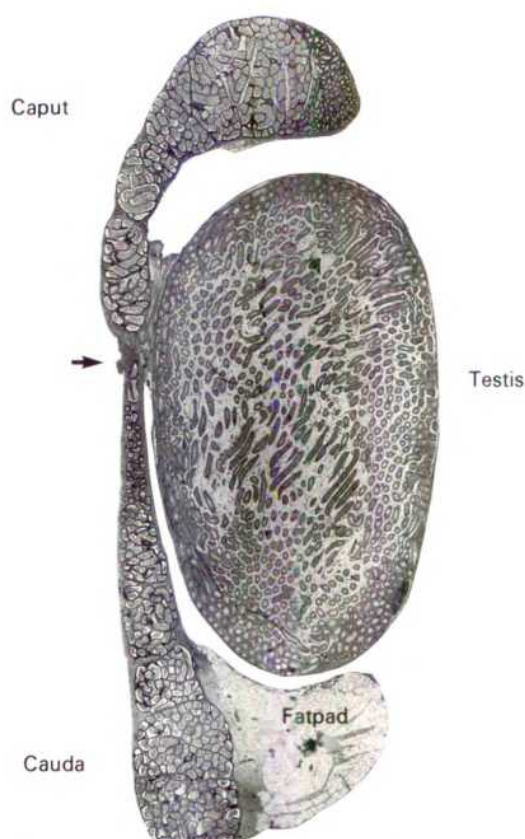


Fig. 2 Longitudinal section through epididymis and testis from a rat with functioning epididymoepididymostomy showing the region of anastomosis (arrow) and confirming the presence of spermatozoa throughout the duct. ($\times 4$).

didymal microsurgery in men with obstructive azoospermia, there is no obstructive dilatation of the duct. Adding to the technical difficulties of this procedure, the rat is an unforgiving model for surgery in that, as shown in this and previous studies (Kuwahara and Frick, 1975), sperm granulomata form readily and obstruction is quickly followed by testicular "shut down" and cessation of spermatogenesis. Such findings were confirmed at laparotomy in those rat operations which had failed totally and also in rats nos 4 and 6 which failed to sire second litters. A reasonable explanation for the initial fertility success and then failure in the latter 2 animals was either that the surgical procedure had been unsuccessful and the litters which were sired 4 months after surgery were produced from spermatozoa already present in the epididymis below the E/E site, or that the E/E had been successful initially but, for reasons unknown to the authors, had subsequently become ob-

structed, causing infertile matings at the second trial.

In contrast, the rabbit has several distinct advantages as an experimental model. Firstly, the duct is of a larger diameter and therefore easier to anastomose. Secondly, the rabbit testis behaves in a manner which is more similar to that of the human testis in that testicular function appears to be able to continue in spite of the presence of epididymal obstruction. Because of these factors further work will be carried out on rabbits, as we feel that we now have a potential model which can be used to study the function of specific areas of the epididymis.

What potential clinical applications are there for epididymoepididymostomy? The criterion of Krylov and Borovikov (1984) for performing this procedure was the finding of localised blockages in the epididymis with sufficient healthy epididymis distal to the site of obstruction to make it possible to perform an epididymoepididymostomy rather than a vasoepididymostomy. Most of their patients (13/19) had post-infective epididymal blockages, but 2/19 patients had a history of trauma and in 4/19 cases the aetiology was obscure. Krylov and Borovikov (1984) found that in 2 cases of obscure aetiology, the site of obstruction was found to be at the junction of the corpus and cauda epididymidis where a single tubule perforating an interlobular septum was found to be obstructed. They referred to this as "the isthmic tubule" and after an epididymoepididymostomy, sperm returned to the semen. Unfortunately, they were unable to follow these patients up sufficiently to determine the long-term outcome of surgery. Since we have not seen a similar case in over 400 explorations for obstructive azoospermia it appears that this developmental anomaly is less common in occurrence than congenital absence of the ductuli efferentes, of which we reported 9 cases from our patient series (Temple-Smith and Southwick; in preparation).

The microsurgical technique of Krylov and Borovikov (1984) causes minor disruption of the neurovascular structure of the epididymis. However, the success of other vasoepididymostomy techniques, in which the epididymis is transected completely, would suggest that as long as an accurate anastomosis has been performed, transection of the epididymis does not decrease the likelihood of a successful outcome (Silber, 1980a and b, 1988). The success of distal vasoepididymostomy in the experimental situation in rabbits has shown that the cauda epididymidis can be bypassed without significantly reducing fertility (Temple-

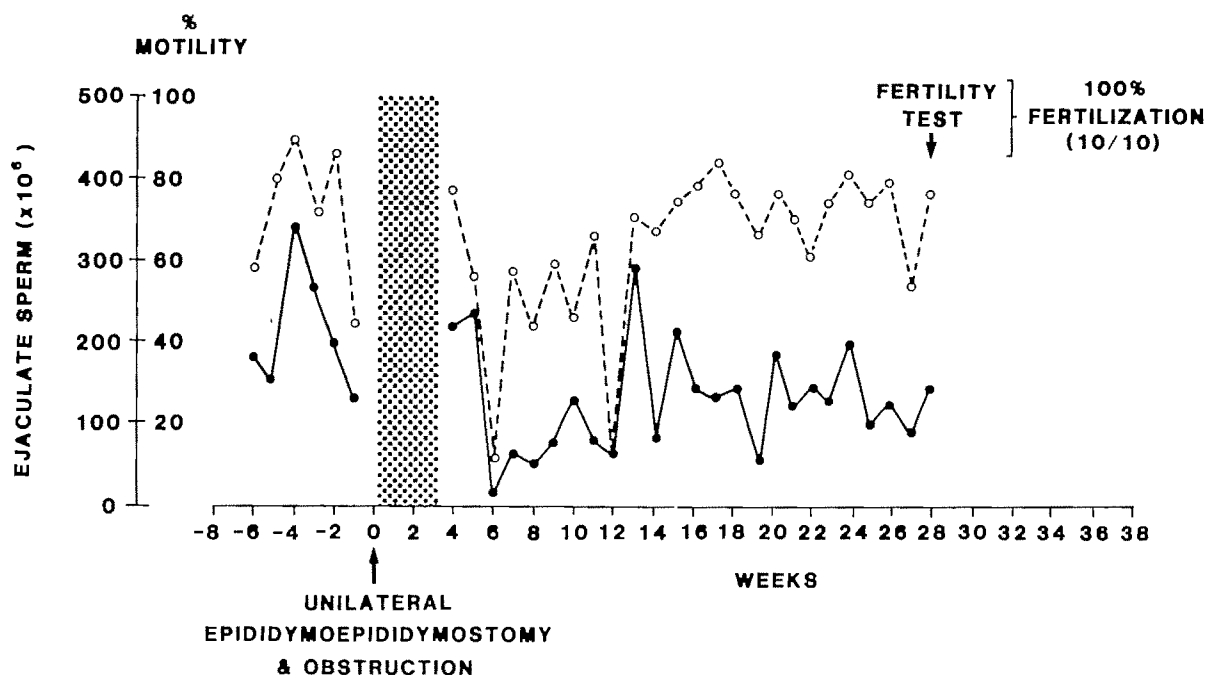


Fig. 3 Pre-and post-anastomosis analysis of semen samples from an adult male rabbit which had undergone successful epididymoepididymostomy. Sperm counts (solid line), % motility (dashed line).

Smith *et al.*, 1989). This is also true in the clinical situation where those patients who have caudal blockage have a good chance of a successful outcome following vasoepididymostomy (Silber, 1978, 1988; Schoysman and Bedford, 1986; Southwick and Temple-Smith, 1988). Epididymoepididymostomy is therefore not considered appropriate for those cases of caudal obstruction where the technically easier vasoepididymostomy has a reasonable chance of success. However, where the site of obstruction is more proximal in the caput epididymidis, the results of vasoepididymostomy both clinically and experimentally are poor, with diminishing fertility and semen quality the more proximally the anastomosis has been placed (Southwick and Temple-Smith, 1988; Temple-Smith *et al.*, 1989). With proximal obstructions where the blockage is limited and more distal regions of the ductus epididymidis appear normal, E/E could be considered as a possible alternative to standard vasoepididymostomy. Even in the special case of Young's syndrome, a common cause of male infertility in the United Kingdom and Australia which presents as obstructive azoospermia in association with chronic respiratory disease, there is no reason to suggest that E/E surgery will not also be applicable. However, as with standard

vasoepididymostomy, which has been successfully used in Young's syndrome patients as well as those with high level epididymal obstruction from other causes, the ongoing disease process in Young's syndrome is likely to contribute to a higher post-operative failure rate in this group (Southwick and Temple-Smith, 1988).

While further development of microsurgical techniques is desirable to enhance the success rates of E/E surgery in the rat and rabbit, this study has shown that E/E has a potential application for improving our understanding of the maturation function of the epididymis—by selectively bypassing specific regions of the epididymis—and also for clinical situations where it may help to improve the fertility chances of selected groups of patients with obstructive azoospermia. Although the caput region of the rabbit and rat epididymis differs in structure from that of man (de Kretser *et al.*, 1982), which consists mostly of convoluted segments of the ductuli efferentes, it seems unlikely that these differences will make these techniques any less relevant or more difficult to apply. This is supported by the fact that current vasoepididymal surgery for caput level obstructions of various aetiologies, including Young's syndrome, has been successfully used with similar results in man and in animal

models such as the rabbit (Southwick and Temple-Smith, 1988; Temple-Smith *et al.*, 1989).

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Seminal White Blood Cells in Men with Urethral Tract Infection. A Monoclonal Antibody Study

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Summary—Monoclonal antibodies were used to detect seminal leucocytes in 19 men with urethritis. A wide range in the number and type of leucocytes between individuals was documented (median $2.06 \times 10^6/\text{ml}$, range $0.6 - 29.89 \times 10^6/\text{ml}$); 22% of the men had $< 1 \times 10^6$ leucocytes/ml. The results suggest that the threshold of $\geq 1 \times 10^6/\text{ml}$ proposed by the World Health Organisation to indicate genital tract infection is unsuitable for men with urethritis.

Male genital tract infections can be difficult to diagnose owing to a lack of clear clinical, bacteriological and seminal fluid criteria (Barratt *et al.*, 1988; Wolff and Anderson, 1988a, b; Micic *et al.*, 1989). The accurate detection of genital tract infection is of great importance because the adverse effects upon fertility of many sexually transmitted pathogens in the male (Fair and Sharer, 1986; Guillet-Rosso *et al.*, 1987; Megory *et al.*, 1987) and female (Sweet *et al.*, 1987; World Health Organisation—WHO, 1987; Paavonen and Wolner-Hanssen, 1989) are now well documented, although a more definite association between infection and infertility is apparent in women than in men (Paavonen and Wolner-Hanssen, 1989). The main seminal fluid criterion consistently used to indicate a genital tract infection is a seminal white blood cell count $\geq 1 \times 10^6/\text{ml}$ of semen (Comhaire *et al.*, 1980). However, the validity of this threshold can be questioned by a critical evaluation of the literature (Barratt *et al.*, 1988). Undoubtedly one of the primary reasons for the conflicting data on the relationship between genital infection in the male and seminal white blood cells (WBCs) is the absence of a reliable, accurate method for the detection and quantification of these cells.

The techniques widely used both in the past and present to detect seminal WBCs are phase contrast microscopy and the benzidine-cyanosine stain (peroxidase method) (Barratt and Cohen, 1987; Barratt *et al.*, 1989b). Using phase contrast microscopy, it has been suggested that > 5 million WBCs/ml of semen are indicative of a pathological change (Barratt *et al.*, 1988). Comhaire *et al.* (1980) examined 500 men from infertile couples for male accessory gland infection and demonstrated that in ejaculates containing $> 1 \times 10^6$ peroxidase positive leucocytes/ml of semen there were significantly more pathogenic bacteria than in the group with $< 1 \times 10^6$ peroxidase positive leucocytes/ml. In contrast, Monteiro *et al.* (1987), using urethral swabs and isolating the pathogenic organisms when present, failed to demonstrate a significant relationship between active urethral infection in 36 potential donors and seminal WBCs detected using the peroxidase method. Berger *et al.* (1982) could find no significant relationship between a positive bacterial culture and number or concentration of WBCs in semen.

Now more sophisticated and accurate techniques to detect leucocytes, e.g. monoclonal antibodies (MAbs), are available (Barratt *et al.*, 1990a). El-Demiry *et al.* (1986), using such antibodies, reported no significant relationship between the growth of micro-organisms in semen and the

number or type of WBCs, although such men had no clinical signs of infection. Wolff and Anderson (1988a), also using monoclonal antibodies, reported significantly higher numbers of total leucocytes, CD4⁺ lymphocytes and monocytes/macrophages in men with high levels of granulocyte elastase in seminal plasma (1000 mg/ml—which is indirectly associated with a genital infection) compared to samples with low levels of granulocyte elastase (Micic *et al.*, 1989). However, no clinical indication of infection or microbiological analysis was presented.

The aim of this study was to determine, using monoclonal antibodies to the seminal white cell populations, the concentration and types of WBCs in the semen of men with clinically diagnosed urethral tract infections.

Patients and Methods

Patients with active urethral tract infections were recruited, following investigation, from the Department of Genito-Urinary Medicine, Royal Hallamshire Hospital, Sheffield, and the Department of Genito-Urinary Medicine, University College Hospital, London. All patients were recruited and examined by the same doctor (A.R.). Twelve were diagnosed as having non-specific urethritis (NSU: no organisms isolated), 5 had chlamydial urethritis and 2 had gonococcal urethritis. In total, semen samples from 19 men were examined.

Semen samples

All semen samples were produced by masturbation into sterile plastic containers (approximately 1–5 h after clinical examination). The samples were left for approximately 30 min at 37°C to liquefy. After liquefaction, they were assessed for sperm concentration and round cell count at standard dilutions (1 in 10, 1 in 20, 1 in 100 as appropriate) using phase contrast microscopy at x 400 magnification and a Neubauer counting chamber (Barratt *et al.*, 1989a). The samples were also assessed for motility (graded into 1: rapid linear progression; 2: slow linear progression; 3: no forward progression; 4: immotile). The presence of sperm bound antibodies or seminal plasma antibodies was examined using either the direct or the indirect immunobead test respectively (Barratt *et al.*, 1989a). The semen smears were subsequently analysed with the aid of monoclonal antibodies to elucidate the WBC populations (Barratt *et al.*, 1990b).

Preparation of semen smears for leucocyte staining

Liquefied semen was washed twice in phosphate buffered saline (PBS, Dulbecco, Oxford) at 600 x g to remove the seminal plasma. The resulting cell pellet was resuspended in PBS to approximately 50 million spermatozoa/ml. After gentle vortex mixing to ensure homogeneity, 10- μ l aliquots of the resulting suspension were spotted on to pre-marked Poly-L-Lysine (PLL Sigma Chemical Co., Poole, Dorset) coated slides. The spots were allowed to air dry for 2 h and the material was then fixed in acetone for 10 min. The slides were wrapped in aluminium foil and stored at –20°C.

Monoclonal antibodies and immunological staining of leucocytes

A panel of commercially available documented MAbs was used to detect the white blood cells in the semen smears and control slides (Barratt *et al.*, 1990b). The primary mouse anti-human MAbs used in this study were HLe-1 (all leucocytes) anti Leu 2a (cytotoxic/suppressor T lymphocytes), anti Leu 3a (helper/inducer T lymphocytes), anti Leu 12 (B lymphocytes) and anti Leu M3 (monocyte/macrophages) (Becton Dickinson, Cowley, Oxford). The secondary peroxidase conjugated rabbit anti-mouse immunoglobulin was supplied by Dakopatts (High Wycombe).

Leucocyte subpopulations on thawed slides were detected by the indirect immunoperoxidase techniques as previously described (Barratt *et al.*, 1990b). Essentially, 10- μ l aliquots of anti-leucocyte MAbs (diluted 1:50 in PBS) were incubated on the fixed semen spots. The spots were then incubated with the peroxidase conjugated rabbit anti-mouse secondary MAb (diluted 1:30 in PBS). Visualisation of the bound antibody and therefore the leucocytes was enabled by incubating the slides with diaminobenzidine (0.6 mg/ml) hydrogen peroxide (0.01% v/v) substrate for 5 min (Sigma Chemical Co., Poole). The slides were counterstained with haematoxylin, dehydrated and mounted in DPX.

Controls

Positive and negative controls were included in each batch of slides stained. Peripheral blood leucocytes (PBs) were separated from whole blood using Histopaque density gradients (Sigma Chemical Co., Poole) and the prepared PBs were then fixed to PLL coated slides. Positive controls were PBL slides stained with both primary and secondary

MAbs; in the case of negative controls the primary antibodies were omitted.

Evaluation of stained slides

All of the slides were read by the same operator. Brown, MAb stained leucocytes and blue haematoxylin stained spermatozoa were counted using an Olympus BH 2 microscope using brightfield illumination (NA=0.8) at $\times 1000$ magnification. The concentration of MAb stained leucocytes/ml of ejaculate was calculated using the following formula:

$$\text{Number of leucocytes/ml} = \frac{\text{number of brown cells in 10 fields}}{\text{number of sperm in 10 fields}} \times \text{original sperm concentration}$$

Investigation procedure at the Department of Genito-Urinary Medicine

A detailed history was taken with particular reference to previous genital infection and trauma, followed by clinical examination of the genitalia. A urethral smear was then taken, Gram stained and examined for the presence of *Neisseria gonorrhoea* and white blood cells. Non-gonococcal urethritis was defined as > 5 WBCs/high power field ($\times 400$) with negative cultures for gonococcus. A swab was then taken and placed in transport medium for subsequent investigation for *Chlamydia trachomatis* by ELISA ('Chlamydiazyme', Abbot).

Serum samples from the men were examined for antibodies to *Treponema pallidum* (syphilis).

Statistical analysis

A Mann Whitney U Wilcoxon rank sum W test was used to detect any significant difference between WBC types and seminal parameters between the groups. A Spearman's rank correlation coefficient was used to assess the correlation between WBC types and genital infection or semen parameter. All analyses were performed using the SPSSX package on the University of Sheffield IBM 3083 Computer.

Results

White blood cells were detected in all semen samples with a wide range in the concentration and subtypes between individuals (Table 1). Of the 19 samples, 15 had $> 1 \times 10^6$ WBCs/ml of semen. Both men with gonococcal urethritis and all 5 men with chlamydial urethritis had $\geq 1 \times 10^6$ WBC/ml se-

Table 1 Seminal White Blood Cells ($\times 10^6$ /ml) in Semen of Men with Active Urethral Infection

	Median	Range
Total leucocytes	2.07	0.16-29.89
Monocytes/macrophages	0.56	0.09-21.52
Suppressor/cytotoxic T cells	0.15	ND-3.6
Helper/inducer T cells	0.06	ND-5.33
B cells	ND	ND-0.66

ND = none detected.

men; however, 4 of the men with NSU (no organism isolated) had $\leq 1 \times 10^6$ WBC/ml semen. In all but 1 ejaculate, monocytes/macrophages were the predominant WBC type. In 13 of the 19 men more suppressor/cytotoxic T cells than helper/inducer T cells were recorded. In 3 men these ratios were approximately the same.

Table 2 shows a wide range of the total number of WBCs and subtypes not only between the 3 groups of men but also within each group. In the men with chlamydial urethritis there were noticeably higher concentrations of WBCs than in those men with NSU where no organism was isolated. However, there was no significant difference in the concentration of WBCs between the 3 groups of men.

The total numbers of WBCs in the 2 men with gonococcal urethritis were very different from each other. In both of these ejaculates most of the cells detected by the pan leucocyte marker (Hle 1) were identified by the MAb panel. However, in the men with NSU (no organism isolated) only a mean of 31% of the cells detected by the pan leucocyte marker were detected by the MAb subtypes and in the men with chlamydial urethritis only 16% were detected by this panel (Table 2).

None of the semen samples had antisperm antibodies. There was no significant correlation between any of the documented semen parameters and the white blood cell types (Table 3).

Discussion

This study shows a wide range in the number, concentration and type of seminal white blood cells in men with active urethral infection (Tables 1 and 2). Since 22% of the men examined had $< 1 \times 10^6$ WBCs/ml of semen, a threshold level of $\geq 1 \times 10^6$ WBCs is not suitable for clinical use in this group.

Previous studies examining the relationship between WBCs in semen and genital tract infection

Table 2 Seminal White Blood Cells ($\times 10^6/\text{ml}$) in Semen of Men with Non-specific Urethritis, Chlamydial Urethritis and Gonococcal Urethritis)

<i>Leucocytes</i>	<i>Non-specific Urethritis (no organisms isolated) Median (range)</i>	<i>Chlamydial urethritis Median (range)</i>	<i>Gonococcal urethritis Median (range)</i>
Total leucocytes	1.52 (0.16–12.6)	4.76 (1.84–17.17)	15.71 (1.73–29.89)
Monocytes/macrophages	0.28 (0.09–1.95)	0.69 (0.41–0.99)	11.07 (0.62–21.52)
Suppressor/cytotoxic T cells	0.16 (ND–1.26)	0.12 (0.02–0.26)	1.8 (ND–3.6)
Helper/inducer T cells	0.06 (ND–0.84)	ND (ND–0.26)	2.69 (0.05–5.33)
B Cells	0.02 (ND–0.22)	ND (ND–0.25)	0.33 (ND–0.66)
No. of men with $\geq 1 \times 10^6$ leucocytes/ml	8/12	5/5	2/2

have produced controversial results (Barrett *et al.*, 1988). Two major reasons for this controversy are the failure to detect the WBCs accurately and the absence of clear clinical criteria to diagnose active infections. In this study, these 2 points were addressed. Firstly, the presence of a genital infection was clinically determined using extensive microbiological screening. This method of screening is more accurate and reliable than using a simple semen culture, which is of limited diagnostic value (Barratt *et al.*, 1988). Secondly, monoclonal antibodies, previously demonstrated to be reliable and accurate in detecting the seminal WBCs series in men (Wolff and Anderson, 1988a, b; Barratt *et al.*, 1990b) were used; the appropriate use of positive and negative controls confirmed this. However, there was a clear shortfall between the number of cells detected by the pan leucocyte

marker (HLe 1) and the sum of the individual monoclonal antibodies to the specific subpopulations (Table 2). This was probably due to the undetected granulocytes. Other authors have also experienced difficulty in detecting granulocytes; for example, Wolff and Anderson (1988) relied on criteria such as "typical granulocyte cell size" and "furry" surface appearance for identification. Our attempts to use commercially available monoclonal antibodies to granulocytes have so far been unsuccessful; although specific for blood granulocytes, they cross react with many anucleate bodies in semen (Smith *et al.*, 1989). This cross reaction makes identification and quantification difficult. The cause of this cross reactivity is unknown but it may be partly due to a cross reactive antigen in seminal plasma which masks the other cells (Thaler *et al.*, 1989). The use of an accurate and reliable

Table 3 Semen Parameters of Men with Non-specific Urethritis, Chlamydial Urethritis and Gonococcal Urethritis

<i>Leucocytes</i>	<i>Non-specific urethritis (no organisms isolated) Median (range)</i>	<i>Chlamydial urethritis Median (range)</i>	<i>Gonococcal urethritis Median (range)</i>
Density ($\times 10^6/\text{ml}$)	22 (07–110)	21 (07–139)	33 (33–34)
Round cell count	03 (01–11)	05 (04–17)	11 (02–20)
Motility (%) I	14 (7–31)	9 (1–29)	27 (27–28)
II	26 (14–36)	28 (17–31)	27 (27–28)
III	17 (11–37)	19 (9–25)	13 (06–22)
IV	36 (20–66)	49 (29–60)	22 (20–25)

granulocyte marker for future research in this area is of great importance.

In this study there were no significant differences between the semen parameters of the 3 groups of men with urethritis (Table 3). In contrast to the unequivocal evidence of an adverse effect of sexually transmitted pathogens on female fertility to date, the evidence of an adverse effect of sexually transmitted pathogens on male fertility is less clear (Paavonen and Wolner-Hanssen, 1989). As tests of sperm function are now readily available, future studies should concentrate on documenting the effect of an active infection on sperm function and future fertility potential, and not concentrate on measuring traditional semen parameters as these are poor indicators of fertility.

None of the men had sperm bound antibodies or antibodies in their seminal plasma. This contrasts with the results of Witkin and Tooth (1983), who reported that 48% of infertility patients with seminal culture positive asymptomatic infections had antibodies in seminal plasma; however, the nature of the infection, if present, was undetermined and the technique used to detect the antibodies may produce false positive results (Clarke, 1988). Shahmanesh *et al.* (1986) detected serum antisperm antibodies in only 16% of patients with clinically diagnosed urethritis. The titres in some men increased with time. In the present study, serum samples were not tested for antisperm antibodies and we obtained only 1 semen sample, so are unable to comment on the possible latent development of antisperm antibodies in these men.

Concordant with the results of other studies on seminal WBCs, a wide range in the number of WBCs in the ejaculates between individuals was noted (Tables 1 and 2). Wolff and Anderson (1988a), using similar monoclonal antibodies, reported median total numbers of leucocytes of 170,000 (range 8970–20,520,000) per ejaculate in fertile men and 1,035,000 in men attending an infertility clinic (range 43,120–104,580,000). In the present study the median number of WBCs overall was $2.06 \times 10^6/\text{ml}$ (range 0.16–29.89), which is higher, although not significantly so, than the median level in our fertile semen donors who are free from genital infections and have no antisperm antibodies (median $0.81 \times 10^6/\text{ml}$, range 0.16–16.06, $n=18$) (Barratt *et al.*, 1990a).

With 22% of the men with active urethral infection having $<1 \times 10^6$ WBC/ml of semen, a threshold level of $\geq 1 \times 10^6$ WBC/ml is clearly an unreliable indicator of urethral infections. However, the median levels of WBCs in the men with

chlamydial urethritis and gonococcal urethritis were all $>1 \times 10^6$ WBC/ml of semen; therefore, although there was large individual variation, a putative threshold level may apply to these 2 groups. Data from Wolff and Anderson (1988a) demonstrated significantly higher numbers of white blood cells, detected using monoclonal antibodies, in men with indirect evidence of genital infection (elastase levels in seminal plasma >1000 ng/ml) (Wolff and Anderson, 1988a; Micic *et al.*, 1989); thus a threshold level may be proposed. However, to examine further the relationship between genital tract infection and seminal WBCs it is necessary to determine the number and type of WBCs in different groups of men with clinically diagnosed infections, *e.g.* prostatitis and epididymitis. More valuable diagnostic information than the total number, or concentration, of WBCs may be provided by an examination of the types of WBCs in semen. In this study the pathogen isolated (*Chlamydia*, gonococcus) had a notable influence on the number and types of seminal WBCs detected. For example, in the men with chlamydial urethritis the majority of the cells were probably granulocytes, yet in the men with gonococcal urethritis granulocytes were not the predominant subtype. This possibility requires further examination using larger numbers of men (chlamydial urethritis and men with gonococcal urethritis). It would also be of interest to establish the activation status of these cells of men with a genital infection and then progress to determine the cytokines produced by these cells, as such cytokines have previously been reported to affect the function of the spermatozoa (Barratt *et al.*, 1990a).

In conclusion, a wide range in the number and subtypes of seminal WBCs is present in the ejaculates of men with urethritis. Further research should concentrate on these WBC types in other groups of men with clinically diagnosed infections. Specific sperm function tests should be employed to determine the effect of a clinical genital tract infection on male fertility potential.

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The Role of Colour Duplex Ultrasonography in the Diagnosis of Vasculogenic Impotence

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Summary—Colour duplex ultrasonography was used to obtain peak systolic velocity (PSV) readings from cavernosal arteries at rest and during papaverine-induced tumescence. Results from 31 men with vasculogenic impotence were compared with those from 17 men with non-vasculogenic impotence and a control group of 6 potent men.

In the flaccid state no significant differences in PSV readings were found between the vasculogenic and control groups. Following the injection of papaverine, men from the vasculogenic group without venous leakage were alone in having significantly lower PSV readings compared with the potent controls.

All 23 men with normal penile haemodynamics had a mean PSV ≥ 20 cm/s during tumescence. This was also the case for 19 (61%) of the vasculogenic group, including 9 (69%) of the 13 patients with venous leakage. The remaining 12 men in the vasculogenic group (39%) had a mean PSV < 20 cm/s, this being diagnostic of an inadequate arterial inflow.

Colour duplex ultrasonography can identify patients who have marked arterial insufficiency as the major cause of their impotence and hence allows more rational selection for angiography and revascularisation. Lesser degrees of arterial deficit are difficult to characterise using mean PSV readings alone.

Most men with erectile failure presenting in middle age will have a vascular cause (Virag *et al.*, 1985). In theory this may be the result of either arterial, venous or sinusoidal abnormalities or any combination thereof. Normal penile haemodynamics are a prerequisite for a complete erectile response to intracavernosal vasoactive drugs such as papaverine. However, lesser responses can result from strong psychogenic inhibition as well as vascular disease (Buvat *et al.*, 1986).

The initial investigation used to assess men with suspected vasculogenic impotence is cavernosometry/cavernosography, which will diagnose failure of venous occlusion (Wespes *et al.*, 1986). The arterial component of the erectile mechanism is more difficult to assess, as is illustrated by the variety of methods currently used such as the penile/

brachial index (PBI) (Abelson, 1975), Xenon-133 washout (Haden *et al.*, 1989) and pudendal angiography.

Duplex ultrasonography, in combination with intracavernosal papaverine, has been used to image the cavernosal arteries and simultaneously record Doppler waveforms during tumescence (Lue *et al.*, 1985; Robinson *et al.*, 1989). Initial difficulties in vessel identification and maintenance of the optimal Doppler angle have been overcome by the addition of colour flow technology (Quam *et al.*, 1989).

A critical mean peak systolic velocity value during tumescence of 25 cm/s has been postulated (Lue *et al.*, 1989), lesser readings being diagnostic of arterial disease.

Against this a recent study of arterial velocities during papaverine-induced erection in potent volunteers found lower PSV values in 2 (29%) of the 7 men investigated (Schwartz *et al.*, 1989).

This study was performed to assess further the role of colour duplex ultrasonography in the management of men presenting with erectile failure.

Patients and Methods

The study was approved by the Newcastle Joint Ethics Committee prior to its commencement. Included in the study were 48 men referred to the out-patient department with erectile failure (age range 34–72 years, mean 54). Initially a full history was taken and a relevant physical examination performed. Abnormalities of the pituitary-gonadal axis were excluded by measurement of serum testosterone, gonadotrophins and prolactin. The clinical response to intracavernosal papaverine was then assessed visually and by palpation. A complete response was defined as the presence of penile rigidity resulting in an erection $>90^\circ$ when standing. Patients who experienced lesser degrees of tumescence despite a maximal papaverine dose of 60 mg underwent pharmacocavernosometry/cavernosography using a standard technique. The right corpus cavernosum was cannulated and 60 mg of papaverine injected; saline was then infused at increasing flow rates to a maximum of 100 ml/min. Failure to produce an erection indicated venous leakage, which was then confirmed by cavernosography.

Six potent men suffering from mild Peyronie's disease were also included in the study as a control group to provide normal data (age range 24–55 years, mean 41). All 6 experienced natural erections of normal rigidity and had penile curvatures $<45^\circ$.

Colour duplex ultrasonography of both cavernosal arteries was then performed on each of the 54 subjects, using an Acuson 128 scanner with a 5 MHz imaging transducer. The optimum site for Doppler recording was found to be on the dorsal surface of the penis just distal to the pubis, the transducer being placed transversely and angled towards the penile root. Each artery was imaged at this site and Doppler waveforms recorded, first in the flaccid state and then 5 and 15 min after the intracavernosal injection of papaverine. Patients known to respond fully were given their established effective dose; the 6 potent men received 30 mg, whilst men with vasculogenic impotence were given 60 mg.

Peak systolic velocity readings in cm/s were taken from the recorded waveforms and expressed as mean (± 1 SD) for each diagnostic group.

Statistical analysis was performed using Student's *t* test, the level of significance being taken as $P < 0.05$.

In addition, the mean peak systolic velocity following papaverine (the average of the PSV readings from right and left cavernosal arteries) was calculated for each subject. This was then compared with critical velocity values of 25 and 20 cm/s.

Results

On the basis of clinical findings, response to papaverine and results of cavernosometry, the 48 men were classified as having vasculogenic or non-vasculogenic impotence (Table). We were able to identify and record waveforms from 101/108 cavernosal arteries at rest (94%) and all but 1 artery (99%) during tumescence.

In the flaccid state there was no significant difference in PSV values between the control group (13.3 ± 7.2 cm/s) and those with suspected arteriogenic impotence (11.9 ± 6.3 cm/s). This was also the finding in men with venous leakage (16.3 ± 10.7 cm/s) and in those with psychogenic impotence (11.2 ± 4.6 cm/s). Higher readings were obtained from men with neurogenic impotence (18.3 ± 11.2 cm/s) but this did not reach statistical significance.

Following intracavernosal papaverine, velocities increased in all but 1 subject; the exception had a fall in velocity associated with a markedly damped waveform. In 39 men (72%) peak systolic velocities were maximal at 5 min, whereas in the remaining 15 men higher readings were obtained at 15 min. The right and left cavernosal arteries commonly showed a degree of asymmetry in PSV readings before and after papaverine; this finding was noted in all diagnostic groups.

Table Aetiology of Impotence in 48 Men

<i>Clinical Aetiology</i>	<i>No.</i>
Neurogenic	6
Psychogenic	11
Total non-vasculogenic	17
Venous leakage	13*
No venous leakage (Suspected arteriogenic)	18†
Total vasculogenic	31

* Includes 3 diabetics.

† Includes 5 diabetics.

During tumescence, PSV readings from men with suspected arterial insufficiency (20.8 ± 10.4 cm/s) were significantly lower ($P < 0.05$) than the values recorded in the control group of potent men (32.2 ± 17.3 cm/s). Readings from those with venous leakage (26.0 ± 14.7 cm/s), psychogenic impotence (34.6 ± 16.6 cm/s) and neurogenic impotence (45.3 ± 19.3 cm/s) did not differ significantly from the normal values.

There were 26 patients with a mean PSV < 25 cm/s following papaverine. Five (19%) of these developed a full erection in response to papaverine, 8 (31%) had venous leakage and 13 (50%) were thought to have arteriogenic impotence. By comparison, of 12 patients with a mean PSV < 20 cm/s none was haemodynamically normal, 4 (33%) had venous leakage and the remaining 8 (77%) were presumed to have arteriogenic impotence.

A post-papaverine mean PSV ≥ 20 cm/s was recorded in 19 (61%) of the men classified as vasculogenic, of whom 9 had venous leakage on cavernosography. The remaining 10 men without evidence of venous pathology included 5 (63%) of the 8 diabetics studied.

Papaverine-induced erection was prolonged (> 4 h) in 1 patient; this was successfully managed by simple aspiration. No other complications were encountered.

Discussion

Colour duplex scanning allows rapid identification of cavernosal arteries together with accurate Doppler waveform recording both at rest and following intracavernosal papaverine. In this study, repeated rather than single scans during tumescence were necessary to ensure that maximum velocities for each patient were recorded. The widespread finding of asymmetrical responses of the right and left arteries during tumescence is interesting. It presumably illustrates that the overall supply is freely shared between the 2 corpora and suggests that unilateral arterial disease is unlikely to cause erectile failure. Previous studies have used arterial diameter changes as part of their diagnostic criteria (Lue *et al.*, 1989). We felt that the small measurements involved (0.1–2 mm) were at the lower resolution limit of the 5 MHz transducer, leading to potentially large errors. We therefore did not attempt to record such data.

Other investigators who have previously used duplex ultrasound without colour have been unable to reliably image the cavernosal arteries at rest

(Robinson *et al.*, 1989). The use of colour flow mapping has enabled us to locate and record waveforms from 94% of the arteries studied in the flaccid state. The lack of differences in PSV readings so obtained must cast doubt on the usefulness of static measurements such as the PBI in the investigation of vasculogenic impotence. The relatively high readings found in patients with neurogenic impotence at rest implies a loss of sympathetic tone in the cavernosal arteries. This could also account for the high sensitivity to papaverine that such patients exhibit. By contrast with our findings in the flaccid state, men with arteriogenic impotence suspected from their initial assessment had significantly lower PSV values during tumescence compared with those found in the control group of potent men. This finding directly implicates arterial disease as a major factor in the causation of their impotence. As expected, PSV readings from men without evidence of an arterial deficit were similar to those recorded in the control group, men with neurogenic impotence again having the highest values.

The characterisation of a normal arterial response during papaverine-induced tumescence is difficult. In the present study, 5 men who developed a full erection had a mean PSV < 25 cm/s, including 1 potent man with Peyronie's disease. The usefulness of this criterion in the diagnosis of arterial insufficiency is therefore limited (predictive value 72%). From our results, mean PSV values < 20 cm/s do reliably indicate arterial disease (predictive value 100%). Using this criterion 4 of the 13 men (31%) with venous leakage had concomitant arterial insufficiency and therefore would not have been expected to benefit from venous ligation alone. A more appropriate line of management for such patients might be angiography followed by a combined arterial and venous procedure. As a result of our colour duplex findings, 5 of the 8 men with a mean PSV < 20 cm/s and no evidence of venous leakage have undergone selective pudendal angiography which demonstrated significant distal stenoses/occlusions in every case. These men have since undergone a revascularisation procedure.

Cavernosometry remains necessary for men with a poor erectile response to papaverine but whose mean PSV is ≥ 20 cm/s, thus indicating an adequate arterial inflow. If a venous leak is found in such a case, ligation is likely to restore potency. We found that 10/19 such patients (53%) had no leakage on cavernosometry and therefore no definite diagnosis could be made. It is possible that strong psychogenic inhibition was limiting their response to papaver-

ine; alternatively, isolated sinusoidal disease could be causing their erectile failure. Our finding that 5 (63%) of the 8 diabetics studied fell into this category supported the latter theory, since the prevalence of microangiopathy in various organs is known to be high in middle-aged diabetics (West, 1978). In addition, endothelium-dependent relaxation of cavernosal smooth muscle *in vitro* has recently been shown to be impaired in impotent diabetic men from this age group (Saenz de Tejada *et al.*, 1989).

In conclusion, colour duplex ultrasonography of cavernosal arteries during tumescence accurately determines the increases in arterial inflow that are necessary for penile erection to occur. The use of mean PSV as a measurement of arterial supply is not ideal, considering the wide range of values found in haemodynamically normal men. However, a mean PSV <20 cm/s does indicate a severe arterial deficit irrespective of the presence of venous leakage. We are therefore using the technique to select patients for angiography prior to surgical revascularisation.

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PAEDIATRIC UROLOGY

Urinary Stone Formation in Children with Prenatally Diagnosed Uropathies

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Summary—Among a series of 312 patients with prenatally diagnosed uropathies, 4 male children developed urinary calculi at ages varying from 2 to 5 years. All had upper urinary tract dilatation not associated with vesicoureteric reflux or with renographically defined obstruction; 3 followed *Proteus* urinary infections. Strategies for prevention are discussed.

Fetal uropathies are now commonly detected by prenatal ultrasonography. Among them are examples of upper urinary tract dilatation not associated with vesicoureteric reflux or with obstruction (Rickwood *et al.*, in preparation). As a rule no treatment is required for such cases and the dilatation tends to resolve spontaneously. Nonetheless, 4 of our patients have developed urinary calculi.

Case Reports

Case 1. Male. At 1 month of age investigation of moderate bilateral hydroureteronephrosis that had been detected prenatally disclosed no reflux or bladder outflow obstruction, nor was there ureteric obstruction by the criteria of ^{99m}Tc DTPA diuresis renography (Lupton *et al.*, 1985). Serial ultrasound examinations thereafter were unchanged until, at 2 years of age and following a *Proteus* urinary infection, a calculus was detected distally in the right ureter. This was surgically removed with simultaneous bilateral ureteric reimplantations; per-operative pressure-perfusion studies (Whitaker, 1973) were also negative for obstruction. Four years later the child is free of recurrence, although the degree of ureteric dilatation remains little changed from pre-operatively.

Case 2. Male. Investigation (IVU, ^{123}I Hippuran diuresis renography) of prenatally detected left hydronephrosis showed typical appearances of megacalycosis (Fig. 1), though without obstruction or impaired function. The patient was lost to follow-up until 5 years of age when,

following a *Proteus* urinary infection with haematuria, repeat investigations showed multiple left renal calculi (Fig. 2), though still with unimpaired function. The stones were surgically removed and 18 months post-operatively he is free of recurrence.

Case 3. Male. Moderate hydroureteronephrosis in a solitary left kidney had been detected prenatally. Cystography was normal and there was no obstruction by the criteria of diuresis ^{123}I Hippuran renography. By the age

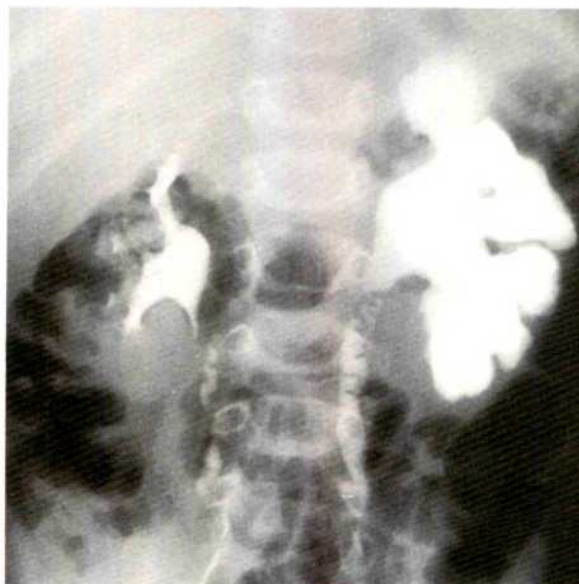


Fig. 1 Case 2. IVU at the age of 1 month shows typical appearances of left megacalycosis.



Fig. 2. Case 2. Plain abdominal radiography at the age of 5 years shows multiple calculi within the left kidney.

of 1 year the dilatation had resolved and remained so a year later. At 2.5 years of age he developed haematuria; urinary culture was sterile, although he had by then received antibiotic treatment. Investigation showed a calculus impacted at the vesicoureteric junction with moderate hydronephrosis. The stone was excised and the ureter reimplanted; 2 years later he is free of recurrence and the upper tract dilatation has resolved.

Case 4. Male. Moderate left hydronephrosis had been detected prenatally. Postnatally there was only mild dilatation; cystography was normal and there was no obstruction by ^{99m}Tc DTPA renography. The dilatation resolved within 6 months and he was discharged when 1 year old. At 3.5 years of age he developed haematuria with a *Proteus* urinary infection. Investigations showed continuing normality of the left upper renal tract. There was a 1-cm bladder calculus and moderate right vesicoureteric reflux. The stone was removed and the right ureter reimplanted; 2 years later he is free of recurrence.

Discussion

Urinary calculi in British children are more common in boys than girls, usually follow *Proteus* urinary infections and are often associated with obstructive uropathies or with vesicoureteric reflux (Johnston, 1982). Their incidence peaks at 1 to 3 years of age. Nowadays they are rare, with some 200 new cases annually in England and Wales (Ghazali, 1975), so that the cumulative risk of a child in these countries developing urinary calculi

by 15 years of age is 0.035%. The 4 cases reported come from a series of 312 infants with prenatally diagnosed uropathies (Rickwood, unpublished data), so that the risk in these patients is evidently far above the norm. Aetiological factors were almost certainly *Proteus* urinary infection plus urinary stasis, yet although these patients were typical in being young, male and having upper urinary tract dilatation, it is curious that the latter was associated neither with obstruction nor with reflux. In the series of 312 cases of prenatally detected uropathies there were 51 patients, predominantly males, with supraventricular obstructions managed conservatively without antibiotic prophylaxis. None of these has developed urinary calculi, nor have more than 40 patients with primary or secondary vesicoureteric reflux. The 4 stone-formers come from a group of 39 patients with non-refluxing, non-obstructive, upper tract dilatation.

Whatever the reason for this phenomenon, it is evident that this last group is at appreciable risk of urinary stones. Could steps be taken to reduce this? Surgical intervention would be difficult to justify in the absence of proven obstruction. Since *Proteus* infection is a major, perhaps essential, factor, low-dose antibiotic prophylaxis could be administered during the period of risk, perhaps to 4 years of age. Alternatively, might there be a role for early circumcision which, it is claimed, reduces 10-fold the chance of urinary infection within the first year of life (Wiswell, and Roscelli, 1986)?

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Surgical Management of Incontinence in Bladder Exstrophy*

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Summary—Between 1978 and 1990, 86 patients with previously closed classical bladder exstrophy and 10 patients seeking undiversion have presented for continence management and have undergone selective reconstruction designed for voiding and/or intermittent urethral catheterisation. The reconstruction in these 96 patients has been reviewed.

Eight of the 10 patients undergoing undiversion achieved a satisfactory state of continence but 4 required Mitrofanoff procedures to enable catheterisation.

Of the other 86 patients, 2 reached a satisfactory state of continence without further surgery; 79 underwent bladder neck surgery for continence either without augmentation ($n=32$) or with augmentation ($n=47$). Twenty of the 32 patients who were treated by bladder neck reconstruction alone were later found to require augmentation. Five patients had very early augmentation either to facilitate neonatal closure or on account of severe upper tract dilatation. Of these, 1 became continent without further surgery and 4 demonstrated the need for bladder neck reconstruction.

Thus 12 children achieved successful continence ($n=6$) or are evolving satisfactorily with potential success ($n=6$) as a result of bladder neck reconstruction.

Of the 71 patients requiring bladder neck reconstruction and augmentation, 68 have completed their surgery. The current status of these patients is: satisfactory in 57 (80%) (42 void/urethral clean intermittent catheterisation (CIC), 7 waiting to learn CIC, 5 Mitrofanoff, 3 artificial urinary sphincter (AUS)). Of the remaining 11 patients (20%), 8 are unsatisfactory to varying degrees and the status of the other 3 is unknown.

Bladder exstrophy remains one of the most difficult surgical challenges in paediatric urology. Historically, most patients underwent urinary diversion after a series of unsuccessful reconstructive surgical procedures. In 1974, D. I. Williams wrote "although functional reconstruction seems the logical treatment and is certainly the one desired by most parents, many urologists are opposed to it on the grounds that the success rate is small, that the children are subjected to multiple procedures and that the complications are by no means negligible with serious urinary infections, pyelonephritis and

stones" (Williams, 1974). Developments, including neonatal closure and reintroduction of osteotomies (Ansell, 1979; Jeffs *et al.*, 1982; Osterling and Jeffs, 1986), a new single-stage epispadias repair (Ransley *et al.*, 1988), bladder augmentation and clean intermittent catheterisation, have all contributed to the improved results of reconstruction reported over the last decade. In this department there has been a firm commitment to reconstruction and no patient with exstrophy has been diverted since 1978.

Between 1978 and 1990, 86 patients with classical bladder exstrophy (excluding cloacal exstrophy, exstrophy variants and epispadias) who have undergone primary bladder closure have presented for continence management. All of these children, plus an additional 10 patients with exstrophy

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presenting for undiversion, have undergone reconstruction designed for voiding and/or intermittent urethral catheterisation. (Undiversions directly to the Mitrofanoff procedure have not been included.) The reconstruction for continence in these 96 patients has been reviewed retrospectively in order to determine the final outcome and the price of this "success".

Patients and Methods

Management of exstrophy

This report is not a comparison of techniques but rather a discussion of how the evolution of new techniques and the timing of surgical steps have been incorporated into continence management of exstrophy by a single surgeon over the last 12 years.

The general philosophy of exstrophy reconstruction over this period has been early bladder closure and annual follow-up until commencement of continence surgery after 4 years of age.

In the late 1970s bladder closure was performed in the first few weeks of life without osteotomies. Subsequently, this evolved to closure without osteotomies limited to the first 24 hours of life and any delayed closures performed with posterior vertical osteotomies.

Following successful closure, annual follow-up consists of cystoscopy and cystography under anaesthesia and ultrasound to assess the development of bladder capacity and status of the upper tracts.

Surgery for continence is undertaken after 4 years of age and once further spontaneous expansion of the bladder appears to have ceased.

Techniques

The principal technique of bladder neck reconstruction has been a 2-layer Young-Dees-Leadbetter procedure (Young, 1919; Dees, 1949; Leadbetter, 1964). Initially performed without modification, it was subsequently altered by the placement of a single sheet of silicone around the reconstructed bladder neck (Diamond and Ransley, 1986). Early patients suffered from erosion of the silicone as previously documented. This led to the current practice of a circumferential omental wrap of the Young-Dees tube and a single layer of silicone Silastic sheet—0.01 in. non-reinforced (Dow Corning, Midlands, USA) loosely arranged around the omentum.

Bladder augmentation has largely been by detubularised cup colocolostomy; 15 to 30 cm of

descending/sigmoid colon were isolated, detubularised and reconstructed as a "cup" before anastomosis to the small bladder element bearing the reimplanted ureters.

In those patients in whom a continent catheterisable stoma had been performed (Mitrofanoff procedure) (Mitrofanoff, 1980), it was created either by using the appendix or distal ureter in conjunction with a transuretero-ureterostomy. Bladder neck closure was performed only if necessary to prevent persistent incontinence.

The single-stage epispadias repair with ventral urethral placement and corporal rotation (Ransley *et al.*, 1988) has been used since 1985 and most of the earlier patients have undergone revision by this method.

The artificial urinary sphincter models used were the AMS-792 and the AMS-800. Exchange of the sphincter cuff for the silicone wrap facilitates its placement.

Assessment of continence

Obtaining an accurate history of continence status is challenging. Descriptive terms have different meanings for different patients and the history may vary from child to parent. Extensive and diligent questioning was carried out in personal interviews in order to make an accurate assessment of continence during the day and at night, at rest and during activity, and to explore the methods employed to cope with each child. It is important to note that the term "cath/void interval" is used to imply the *minimum* interval for emptying which will insure that the child will *always* be dry, not the *average* dry interval.

The state of continence of this group of patients covers a wide spectrum and categorisation is somewhat arbitrary. After reviewing the assessments certain patterns appeared and from these the following classification was derived.

- | | | |
|---|---|--------------|
| <ol style="list-style-type: none"> 1. Excellent: <ul style="list-style-type: none"> —dry day/night/activity —cath/void intervals > 4 h —no restrictions: activity or fluid intake 2. Good: <ul style="list-style-type: none"> —dry day/activity —some night-time wetting —cath/void intervals > 3 h —minor coping methods employed | } | Satisfactory |
|---|---|--------------|

3. Poor: }
 —dry intervals not > 2 h }
 without major effort } Unsatisfactory
 —protection required }
 4. Wet: }
 —continuous leaking }

For simplicity in reporting results in this review, the terms "satisfactory" and "unsatisfactory" are used. These 2 general categories have guided management over the years, with the implication that for groups 3 and 4 further surgery may be required.

Results

Initial Treatment

Ten of the 96 patients in this series were undiverted from ileal or colon conduits and had undergone partial cystectomy. Four of these children achieved a satisfactory state of continence with urethral CIC (3) or voiding with the AUS (1). Four other children were dry but failed urethral CIC and subsequently required the Mitrofanoff procedure. One child is wet and the current status of the other is unknown.

The remaining 86 patients (Fig.) had undergone primary bladder closure between the neonatal period and 3 years of age. The later closures were due to a delay in transfer to this centre. Two of these 86 children reached a satisfactory state of continence without further surgery. Five required early augmentation to enable primary bladder closure or for severe upper tract dilatation. As this was not for continence, bladder neck reconstruction was not performed simultaneously. One of these 5 children achieved "serendipitous" voiding contin-

ence without additional surgery. Three of the 5 subsequently underwent bladder neck reconstruction and 1 is awaiting further surgery for continence. The remaining 79 children underwent bladder neck reconstruction, with or without augmentation, as their primary continence surgery.

Bladder neck reconstruction without augmentation

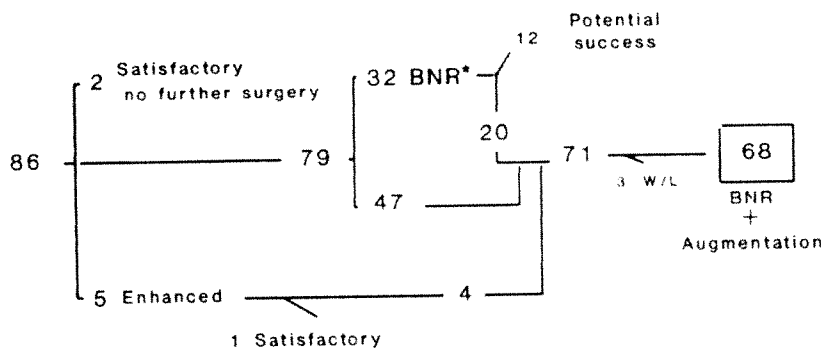
Bladder neck reconstruction alone, without augmentation, was selected for 32 of the 79 patients. This failed to promote development of capacity and continence in 20 patients and augmentation was subsequently indicated. Upper tract dilatation was a significant factor in the decision for augmentation in 9 of these children.

Six of the 32 patients are potentially successful; capacity has progressed but dry intervals currently remain less than 2 h.

Five of the remaining 6 patients achieved satisfactory continence, 3 without further surgery and 2 with the AUS. Two of the 5 need CIC, including one with the artificial sphincter (female). The AUS was used in the one additional patient but subsequent removal was required and a Mitrofanoff procedure was performed.

Bladder neck reconstruction with augmentation

Bladder neck reconstruction with simultaneous augmentation was the treatment of choice in the other 47 patients, 5 of whom had previously undergone bladder neck reconstruction elsewhere. Upper tract dilatation was a significant factor in the selection of 20 of these patients. These 47 patients, plus the 20 who failed bladder neck reconstruction alone in our centre, plus 4 of the 5 who underwent primary augmentation, comprise the group of 71 patients for whom the combination



* BNR = Bladder neck reconstruction.

Fig. Flow diagram of surgical treatment.

of bladder neck reconstruction(s) and augmentation was needed. Three are currently on the waiting list and the other 68 patients have already undergone surgery.

Results in 68 patients with bladder neck reconstruction and augmentation are as follows.

Initially satisfactory. Fifty-five patients (80%) were dry after this surgery. Of the 51 who have remained dry, 41 are voiding and/or on CIC, 6 are waiting to learn CIC (with suprapubic catheters on clamp and release regime), and for 4 who failed CIC the Mitrofanoff procedure was selected. The other 4 later regressed and became wet to varying degrees. One has since become dry with a bladder neck revision. One is waiting for a Mitrofanoff procedure and the other 2 are waiting for further evaluation.

Initially unsatisfactory. Good capacity was achieved in 13 patients (20%) but additional surgery was needed on account of dry intervals being less than 2 h. This included bladder neck revision (2), AUS (3) and Mitrofanoff (1). Two are waiting for the AUS, 2 are hoping for further spontaneous improvement and the present status is unknown for the other 3.

Evolution. The Table summarises the current status of continence and emptying for this group of 68 patients; 43 (60%) are dry and empty by CIC and/or voiding. The AUS and Mitrofanoff procedure served as good alternatives in 8 (10%). In 10 other children (15%) success is anticipated with CIC (7), AUS (2) or the Mitrofanoff procedure (1). Four remain wet to varying degrees and are waiting for further spontaneous improvement or evaluation and the current status is unknown for the other 3.

Anatomical complications. Occlusion of the bladder neck occurred 6 times in 5 patients, 3 prior to the use of combined omental and silastic wrap and in 3 after revision of a previous bladder neck reconstruc-

tion. Removal of silastic was required for infection or erosion in 9 of 47 patients (20%) in the early years but there have been no problems requiring its removal since March 1986, when the placement technique was modified.

Intermittent catheterisation difficulties. So far, 55 children have attempted urethral CIC. Ten of the 11 females achieved it, although minor meatal revisions were required in 3 of them. The other girl was unable to catheterise owing to angulation of the bladder neck which failed to correct after 3 revisions. Of the 44 males, 18 have achieved CIC without technical problems and 11 with additional endoscopic procedure(s) only; 13 required 1 or more urethral revisions and 2 are on the waiting list for a urethral revision. One failed to achieve urethral CIC and required a Mitrofanoff procedure. The majority of the urethral revisions were in boys who had their epispadias repair prior to using the modified technique of ventral urethral placement. Eleven of these 44 boys underwent the new epispadias repair prior to or at the same time as the continence reconstruction and only 1 has required a urethral revision to enable CIC.

Bladder perforation. Delayed spontaneous perforation occurred in 7 patients from 0.5 to 5.3 years (mean 3.3) after augmentation. The history suggested that in 6 patients it was related to indirect trauma with a full bladder and one was due to a catheterisation injury.

Discussion

A discussion of undiversion is beyond the scope of this report. The fact that 4 of the 10 undiverted patients eventually required the Mitrofanoff procedure should not discourage reconstruction designed for urethral CIC or the AUS. However, it should be undertaken only with the clear understanding by the patient and the family that the outcome is less predictable than in patients whose urinary tract remains intact.

Our approach to continence reconstruction for exstrophy has changed over the 12 years included in this review. In the early years, all patients were managed by bladder neck reconstruction alone as the initial continence procedure. The high incidence of upper tract dilatation, the low overall success rate of achieving at least "good" quality continence, as defined in this department, and the years required to evolve to this state were unsatisfactory. From this experience evolved more rigid

Table Bladder Neck Reconstruction and Augmentation: Outcome in 68 Patients

Satisfactory	CIC/void	43	} 80%
	Mitrofanoff	5	
	AUS	3	
	Awaiting CIC	7	
Unsatisfactory	Awaiting AUS	2	} 20%
	Awaiting Mitrofanoff	1	
	Wet/unknown	7	

criteria of selection of bladder neck reconstruction without simultaneous augmentation: bladder capacity > 100 ml and no upper tract dilatation. Of the 65 patients presenting for continence surgery since July 1984, only 13 (15%) have met these criteria. Thus the majority of patients have undergone early augmentation.

It is important to note that augmentation was not performed to "treat" hydronephrosis. Dilatation of the upper tracts was interpreted as an indication that the potential for bladder expansion in response to increased outflow resistance without further risk of renal damage had been reached.

The definition of "satisfactory" continence used in the management of patients in this series is much more rigid than that reported in other reviews of exstrophy reconstruction (Lepor and Jeffs, 1983; Mesrobian *et al.*, 1988; Connor *et al.*, 1989). The child must have 3-h *minimum* dry intervals with *no* episodes of wetting in order to be classified as "good". In fact, continence any less secure than this, with even the occasional accident, has been considered a failure of the reconstructive procedure. It is important to note that *minimum* dry interval has been used rather than *average* (Lepor and Jeffs, 1983). Although either may be an appropriate measure by which the clinician can judge progress, it is only the *minimum* interval that is relevant to the child because it is this by which he/she judges whether or not protection is required. A dry interval of at least 3 h is deemed necessary to satisfy the child, for this allows him/her to cath/void only at breaktime at school when the other children are also being excused. Continence less secure than this demands that the child regularly leave classes in session, wear nappies/pads or have "accidents". It has been noted by parents and children that it is precisely these problems that invoke verbal abuse from the child's classmates. Although a thorough psychological assessment has not been undertaken, it has been observed that all of the significant behaviour problems reported to us in this group of children (varying degrees of social withdrawal and aggressive behaviour) have been related to abuse from their peers.

The combination of bladder augmentation with bladder neck reconstruction has several advantages over bladder neck reconstruction alone. Adequate capacity is achieved immediately and without risk of renal damage from high bladder pressures. In the majority of patients continence develops immediately and the quality of continence achieved is superior to that eventually achieved by bladder neck reconstruction alone. Of the 68 patients who

underwent bladder neck reconstruction and augmentation, 50 (75%) were initially satisfactory and have not regressed; 25 of these even fit the "excellent" category within this already rigid definition of "satisfactory" continence. An excellent state of continence (dry interval > 4 h) affords the child the luxury of catheterising only once during the school day.

The primary problems realised with augmentation have been delayed perforations and the inability to void effectively, which demands intermittent catheterisation. Both apprehension and technical difficulties, especially in the reconstructed male urethra, have caused significant delays in achieving CIC, during which time the children have been managed with suprapubic catheters clamped and then released at intervals of 3 to 4 h. Even though the catheters are changed every 4 to 6 weeks the problem with bladder stones has been significant. However, the children seem to cope better socially being dry with a suprapubic catheter on the clamp and release regime than with wearing nappies during the school years, for the reasons discussed above. Several improvements over the last 2 years have helped to alleviate these long delays in achieving urethral CIC. The addition to the management team of a clinical nurse specialist who is committed to CIC instruction and becomes involved with the children and parents prior to the reconstructive surgery has virtually eliminated the delays due to fear. The new epispadias repair has decreased the technical problems in males.

In the past there has been a strong prejudice towards urethral catheterisation. However, the patients who eventually had the Mitrofanoff procedure have seemed very happy with this. More recently, several males have been encouraged to have a continent catheterisable stoma (Mitrofanoff procedure) in conjunction with conventional bladder neck reconstruction. This avoids prolonged use of the suprapubic catheter if there is a delay in establishing urethral CIC and provides the child with a choice of catheterisation routes. We may learn that the suprapubic route will be preferred in many males. However, the preservation of the urethral route for endoscopic access may be important in the long term.

The AUS has been a useful adjunct to achieving continence in a number of patients but careful selection is critical. Bladder augmentation does not eliminate this as an option but significant instability must be ruled out and, in our opinion, voiding to completion is a prerequisite for males. It appears safe to use urethral CIC in conjunction with the

AUS in females (Gonzalez *et al.*, 1989) and we believe that there may be a wider role for its use in the future.

The omentum and silastic wrap provide vascularised supple support for the Young-Dees tube and an excellent plane for subsequent placement of a sphincter cuff. It is important to avoid wrapping the silastic directly around the bladder neck but instead loosely around the omentum.

The ultimate outcome of reconstruction in patients with bladder exstrophy is a good to excellent state of continence with relatively low morbidity to the upper tracts for all patients, and voiding or intermittent urethral catheterisation (if preferred) for the majority. The price paid has been multiple procedures and admissions to hospital, prolonged use of a suprapubic catheter with its attendant problems while establishing CIC and a risk of delayed bladder perforation. However, these problems have decreased over the period of this review as new developments in management have evolved. Adoption of these new treatments by the surgeon and careful selection for each patient should enable children currently undergoing reconstruction to face a more predictable outcome with a reduced number of surgical procedures and better cosmetic results.

The early experience in this department indicated that the potential of the exstrophy bladder without augmentation to provide satisfactory compliant continence is an unrealistic ambition in the majority of cases and early augmentation may therefore be appropriate in a high proportion of them. However, the long-term outcome of bladder augmentation in children with respect to acidosis (Nurse and Mundy, 1988), somatic growth (Wagstaff *et al.*, 1990), malignant potential (Nurse and Mundy, 1989) and delayed perforation (Elder *et al.*, 1988; Rink *et al.*, 1988) during the course of their lifetime is unknown. Thus it is realised that there is a need for better methods of assessing the potential of the closed exstrophy bladder and more objective criteria for selection for augmentation.

Acknowledgements

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The dedicated care of Sister Valerie Allen and the nursing staff of ward 6CD at the Hospital for Sick Children, Sister Anne Blight and Sister Sue Keeble and the nursing staff of the Children's Ward at the Shaftesbury Hospital, has contributed enormously to the welfare of these children. Sister Brid Carr is to be congratulated on her expertise in counselling and intermittent catheterisation instruction which has brought so many children to a successful outcome.

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Case Reports

Unusual Presentation of a Testicular Tumour

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Case Report

A 31-year-old male presented to the endocrinology clinic with a 3-month history of painful gynaecomastia. He was mildly obese with marked bilateral gynaecomastia and

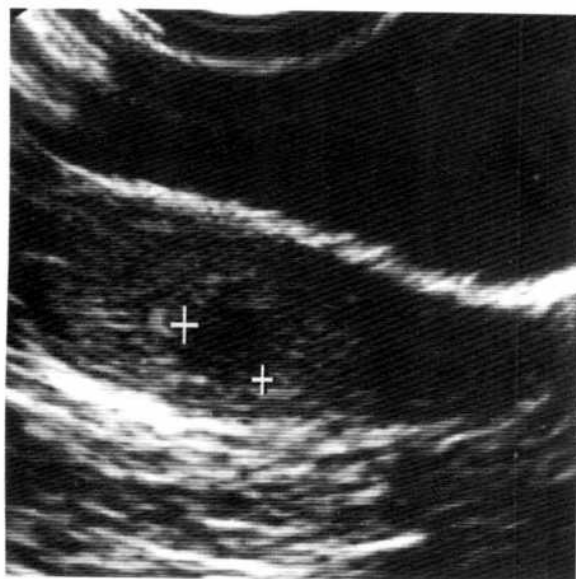


Fig. 1 Ultrasound of the testis.

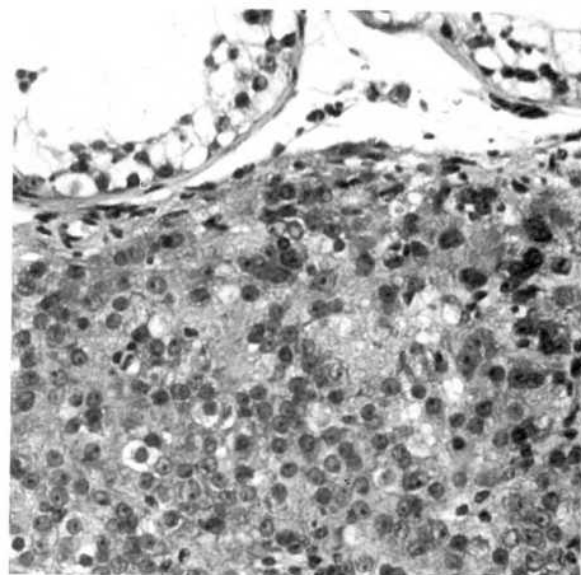


Fig. 2 Representative area of tumour showing typical Leydig cell pattern at low power well delineated from adjacent testicular tubules (top). (H and E $\times 160$).

soft testes 7 ml in volume (normal = 15–30 ml). He had a normal phallus and scrotum with pubic and axillary hair, but no male escutcheon. The rest of his clinical examination was normal. Endocrine investigations revealed oestradiol 230 pmol/l (normal <174), LH 3.5 mU/l (normal = 3–16), prolactin 139 mU/l (normal = 0–800) and testosterone 12.3 nmol/l (normal = 10–38); the sperm count was 70 000/ml (normal > 20×10^6).

Ultrasound of the testes (Fig. 1) revealed a 1-cm hypoechoic area in the centre of the left testis; on venous sampling the left testicular vein oestradiol was 1840 pmol/l (Table). At exploration of the left testis no mass was palpable, but on section of the testis a well delineated grey mass was seen and orchietomy was performed. The testicular mass proved to be a benign Leydig cell tumour (Pugh, 1976) (Fig. 2).

Table Selective Venous Sampling

Site	E_1 (pmol/l)	E_2 (pmol/l)	A (nmol/l)	T (nmol/l)	C (nmol/l)
Inferior vena cava	501	157	1.7	10.6	
Right renal vein	425	112	1.8	9.0	
Left renal vein near vena cava	466	—	1.9	8.1	
Right adrenal	—	113	34.5	7.8	817
Left adrenal	421	135	2	7.1	106
Left testicular	522	1840	3.2	57.3	
Inferior vena cava near opening of right testicular	379	245	1.6	8.0	
Hepatic vein	248	14	0.3	3.0	
Right atrium	379	128	1.7	7.3	
Superior vena cava	461	129	1.4	7.1	

E_1 = Oestrone. E_2 = Oestradiol. A = Androstenedione. T = Testosterone. C = Cortisol.

Comment

The presentation of the testicular tumour in this patient was unusual, for most patients present with a palpable nodule in the testes detectable initially by themselves (Pugh, 1976; Wilson and Foster, 1985). To identify that the testis was the site of the raised oestradiol level we used 2 investigative techniques: testicular ultrasound and selective venous sampling. Testicular ultrasound, which has a resolution of 2 mm in homogenous tissue, proved very helpful in detecting the testicular lesion. Although selective venous sampling (Winters and Troen, 1976) was not diagnostic on its own, the combination of venous sampling data with the ultrasound scan was enough to justify surgery.

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Candida albicans Infection in Solitary Kidney Presenting as Anuria

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Case Report

A 69-year-old man presented with a 48-h history of anuria. He had had a left nephrectomy for calculus hydronephrosis 28 years previously. A plain X-ray film was negative. Renal ultrasound revealed hydronephrosis. The results of tests were as follows: Hb 14 g%, WBC 6000/mm³, blood urea 58 mg%, serum creatinine 2 mg%. A double-pigtail stent was placed without difficulty. Culture of urine revealed *Candida albicans* infection 3 days later. Ureterorenoscopy was performed and *Candida* balls filling the ureter and covering the catheter were observed. Another double-pigtail catheter was inserted and oral medication commenced with sodium bicarbonate and ketoconazole 400 mg/day. Urine culture was sterile after the first week of therapy and the catheter was

removed. Ketoconazole was discontinued after 2 more weeks, when the IVU was normal and repeated cultures were sterile. However, the culture 20 days after discontinuation of therapy showed *Candida albicans* again.

Comment

Candida albicans is a yeast-like fungus which is not a normal inhabitant of the urinary system. Anuria with candida is very unusual. In urinary candidiasis, amphotericin B, flucytosine and ketoconazole are the drugs of choice. Graybill *et al.* (1983) reported successful results with ketoconazole. Our patient was treated with ketoconazole but after therapy ceased, *Candida* was observed again.

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Primary Lymphoma of the Bladder Arising from an Area of Malakoplakia

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A case of primary lymphoma arising in a bladder previously affected by malakoplakia is reported. We believe this is the first case to be described.

Case Report

A 63-year-old lady presented with a 3-month history of frequency, dysuria and haematuria. In the previous 3 years she had had several urinary infections. An intravenous urogram showed a filling defect in the bladder base and cystoscopy revealed irregular mucosal changes on the posterior wall. Biopsies showed features consistent with malakoplakia (Fig. 1). Further biopsies taken 15 months later again showed changes of malakoplakia but now the tissue was heavily infiltrated by lymphocytes.

Eighteen months later the bladder appearances remained the same but biopsies showed non-Hodgkin's lymphoma with no Michaelis-Gutmann bodies (Fig. 2). There was no evidence of lymphomas elsewhere. The

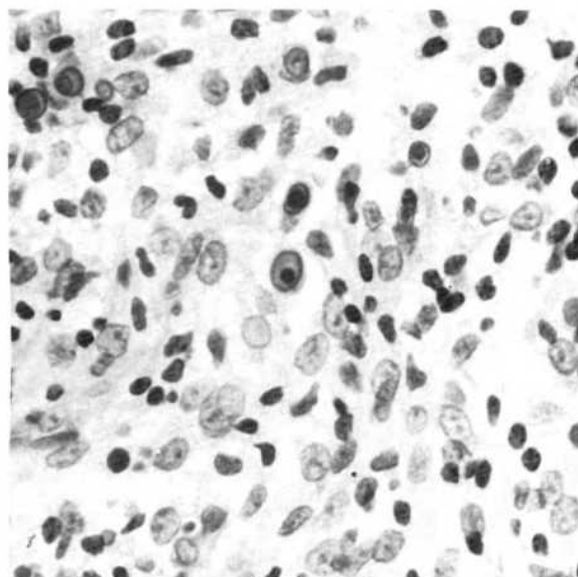


Fig. 1 Initial biopsy showing malakoplakia with macrophages, lymphocytes and Michaelis-Gutmann bodies. (H and E $\times 100$.)

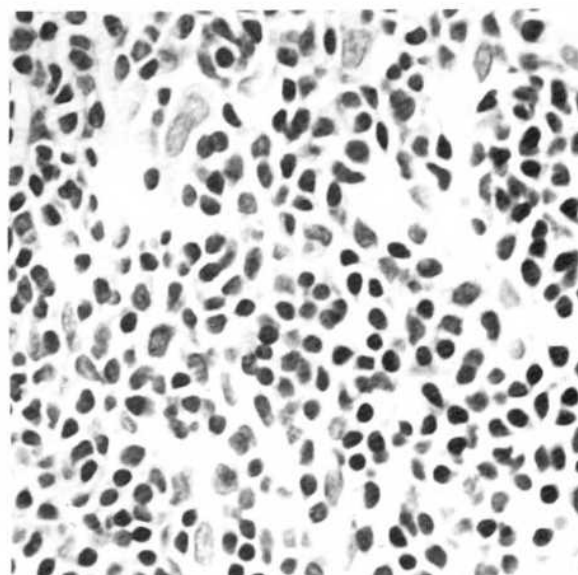


Fig. 2 Bladder biopsy showing a diffuse infiltrate of lymphoid cells consistent with non-Hodgkin's lymphoma. (H and E $\times 100$.)

patient was treated with a radical course of radiotherapy and 3 years later there has been no evidence of recurrence.

Comment

Malakoplakia is a rare granulomatous inflammatory condition which most commonly affects the bladder. The condition is diagnosed histologically by the presence of intracellular and extracellular

Michaelis-Gutmann bodies. Even rarer is primary lymphoma of the bladder. Rosenberg *et al.* (1961) reviewed 1269 cases of primary lymphoma and in only 2 was the bladder involved.

We believe this is the first case described where lymphoma has arisen in a bladder previously affected by malakoplakia. Dervan *et al.* (1986) reported a patient who presented with generalised lymphadenopathy. Histologically the nodes showed the appearance of a lymphoma with Michaelis-Gutmann bodies.

It has been suggested that lymphomas may arise in areas of follicular cystitis or may follow repeated bouts of infection (Curran, 1987).

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Priapism in Haemodialysis Patient due to Prazosin?

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The aetiology of priapism in haemodialysis patients is unclear but the use of heparin during dialysis has been reported to play a role in its induction. We report a patient on haemodialysis in whom we think prazosin, not heparin, was responsible for priapism.

Case Report

A 28-year-old man was admitted with continuous penile erection. He had chronic glomerulonephritis and had commenced haemodialysis at 18 years of age. Two days before admission he experienced prolonged erection and pain during haemodialysis with heparin. The symptoms continued for 2 days. No sexual excitement was apparent. We diagnosed priapism associated with haemodialysis and an Al-Gohorab cavernospongiosum shunt operation

and intermittent pressure on the body of the penis were performed. Six months later there were no major problems. He was receiving 3 mg oral α -blocker (prazosin), 60 mg oral Ca-blocker (nifedipine) and 750 mg oral antisympathetic agent (methyl dopa) for hypertension every day.

Comment

Priapism in haemodialysis patients has been reported in 52 cases. The aetiology is unclear but the relationship between heparin and priapism was first recognised by Duggan and Morgan (1970), who reported 4 cases of priapism in patients receiving heparin following myocardial infarction. Heparin has been considered a major causative factor of priapism in haemodialysis patients but the mechanism is unclear. Fourteen cases of prazosin-induced priapism have been reported since the first 2 cases were described by Bhalla *et al.* in 1979. Our patient received the α -blocker, prazosin. Apart from the report by Branger *et al.* (1985), other studies on haemodialysis accompanied by priapism fail to give details on antihypertensive drugs, including prazosin (Singhal *et al.*, 1986; Banos *et al.*, 1989). We suggest that in patients who have haemodialysis-induced priapism, the use of prazosin should be verified, although heparin cannot be ruled out as the causative factor.

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Partial Extraction of Double-J Stent during Nephrostomy Tube Removal and its Prevention

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Case Reports

Case 1. M.H., a 38-year-old man with 2 calculi in the left renal pelvis, was treated by percutaneous nephrolitho-

tomy. The procedure resulted in successful disintegration and almost complete removal of the stones apart from a few residual fragments. A Malecot catheter was left *in situ* as a nephrostomy tube. Two days later a Double-J stent (Surgitek) was inserted with a view to discharging the patient and readmitting him at a later date for extracorporeal shock wave lithotripsy (Fig. 1). When the nephrostomy tube was removed on the ward, however, the proximal end of the stent was extracted with it. The stent was therefore completely pulled out and a replacement stent reinserted endoscopically under general anaesthesia before discharge.

Case 2. J.S., a 62-year-old man, was transferred to this unit with a left nephrostomy *in situ* for obstructive renal failure from idiopathic retroperitoneal fibrosis. Bilateral Double-J stents (Surgitek) had been inserted and were adequately positioned on plain X-ray (Fig. 2). The nephrostomy tube was no longer required but when it was removed on the ward the proximal end of the Double-J stent appeared with it. A replacement stent was reinserted with considerable difficulty with radiological screening and ureteroscopy.

Comment

A Double-J stent facilitates effective internal drainage with relatively few complications (Pocock *et al.*, 1986). It may be used to replace a nephrostomy when further treatment is delayed (*e.g.* to allow sepsis to settle or renal function to recover) or is not considered (Andriole *et al.*, 1984). Accidental extraction of the Double-J stent is a complication peculiar to removal of the nephrostomy tube. In



Fig. 1 Proximal end entangled with perforations of Malecot catheter.

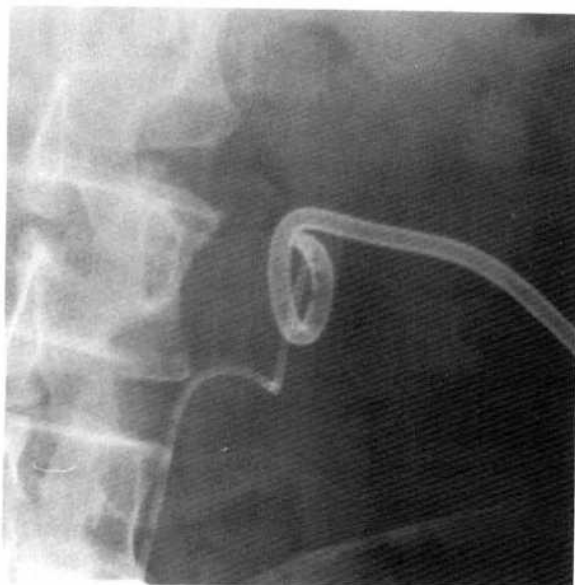


Fig. 2 Proximal end entangled with coil of pigtail nephrostomy tube.

these cases it occurred when the proximal J entangled with the perforations of the Malecot catheter (case 1) and the coil of the pigtail nephrostomy tube (case 2) respectively. In both instances the proximal ends were extruded outside the skin (Fig. 3), requiring complete removal and subsequent replacement. It is conceivable, however, that a "silent" version of this could occur, with the distal



Fig. 3 Double-J stent pulled up with extraction of nephrostomy tube.

end of the stent being withdrawn into the ureter whilst the proximal end is withdrawn into the renal parenchyma or perinephric fat. A ureteroscopy will then be required to remove it and this is not always straightforward. We consider a plain X-ray after removal of a nephrostomy tube when there is a coexistent Double-J stent is imperative. This risk of accidental extraction of a stent can be minimised by inserting the stent under radiological screening; once adequate position is confirmed the nephrostomy tube can be removed under radiological control before extraction of the guide wire from the stent during the same procedure.

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Filling Defects of Infectious Origin in the Cystogram of a 6-year-old Child

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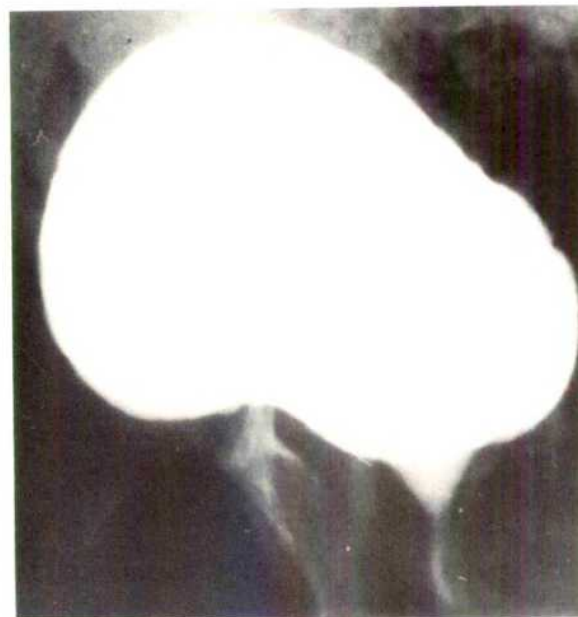
Case Report

A 6-year-old boy was admitted with failure to urinate preceded by a 7-day history of lower abdominal pain.

Physical examination revealed a distended bladder for which urethral catheterisation was required. Urine analysis revealed leucocyturia and haematuria, and culture yielded *Klebsiella*. Cystographic and pelvic ultrasonographic examinations disclosed multiple filling defects on the basal surface of the bladder (Fig. 1). Whole basal and inferolateral surfaces were found to be involved with polypoid masses. Microscopic examination of the biopsy specimen revealed submucosal oedema, dilated vessels and inflammatory reaction which were consistent with cystitis cystica.

After a 14-day course of seftazidim the cystographic and ultrasonographic examinations were normal (Fig. 2).

Cystoscopy 1 month later showed no abnormality.



Comment

Multiple filling defects on cystographic examination initially suggest a malignant origin in children (Dann *et al.*, 1972; Harris *et al.*, 1974). Cystitis cystica, a rare complication of recurrent urinary tract infection, has previously been reported to

cause multiple filling defects (Dann *et al.*, 1972; Harris *et al.*, 1974; Varsano *et al.*, 1975).

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Chronic Urinary Retention Masquerading as Meralgia Paraesthetica

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Case Report

An alert 73-year-old man, in good general health, complained of a burning sensation and pain on the outer aspect of the left thigh for 18 months. He denied any urinary difficulty. Examination by a neurosurgeon disclosed a 15-cm ovoid patch of cutaneous hypoesthesia above the knee (Fig. 1). The diagnosis of meralgia paraesthesia was made. Partial temporary relief was produced by cortisone injections near the lateral attachment of the inguinal ligament. At surgery the fascia lata was incised near the origin of the sartorius muscle and small nerve fibres beneath the inguinal ligament were divided—all to no avail.

Computed tomographic scans of the abdomen revealed massive distension of the urinary bladder extending above the iliac crest (Fig. 2). When 2000 ml of urine were drained from the bladder, the patient experienced prompt and lasting relief of thigh discomfort. Despite resection of 30 g of trilobar prostatic hyperplasia, he continues intermittent self-catheterisation because of an atonic bladder. In retrospect, he feels that perhaps his stream may not have been that strong after all.

Comment

The lateral cutaneous nerve of the thigh derives from L2 and L3 nerve roots. Emerging from the psoas muscle, the nerve travels around the pelvis



Fig. 1 Patch of hypoesthesia in the distribution of the lateral cutaneous nerve of the thigh.

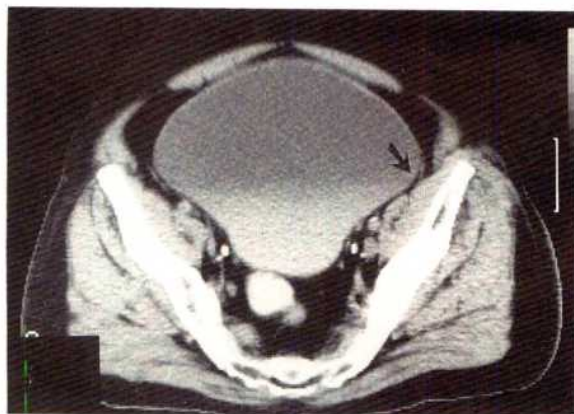


Fig. 2 CT scan showing how the lateral cutaneous nerve of the thigh might be compressed between the massively distended bladder and the iliacus muscle.

on the iliacus muscle. It passes beneath or through the inguinal ligament near the anterior superior iliac spine to distribute branches to the lateral aspect of the thigh as far as the knee.

Paraesthesia in the distribution of the lateral cutaneous nerve of the thigh is known as meralgia paraesthetica. Symptoms are generally attributed to entrapment of the nerve by the inguinal ligament. Compression has been ascribed to obesity, trauma and tight belts or jeans. Pressure on the nerve in its pelvic course may be caused by ascites or pelvic masses such as the pregnant uterus (Ecker and Woltman, 1938). A distended bladder causing a

burning sensation in the thigh is recorded rarely (Amarenco *et al.*, 1987). Chronic urinary retention should be considered as a possible cause of meralgia paraesthetica in the elderly male, even in the absence of voiding complaints.

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Ecker, A. D. and Woltman, H. W. (1938). Meralgia paraesthetica: a report of 150 cases. *J.A.M.A.*, **110**, 1650–1652.

Requests for reprints to: J. J. Pollen, Kaiser Permanente Medical Center, 4647 Zion Avenue, San Diego, California 92120, USA.

Signet Ring Cell Adenocarcinoma of the Ureter

B. DELAHUNT, J. N. NACEY, P. J. MEFFAN and M. G. CLARK, *Departments of Pathology and Surgery, Wellington School of Medicine and Mary Potter Hospice, Wellington, New Zealand*

Case Report

A 75-year-old widow presented with a 3-month history of constant dull pain over the right renal angle. Retrograde ureteropyelography showed obstruction with marked dilatation of the right ureter beyond the pelvic brim (Fig. 1), while an isotope renogram indicated minimal right renal function. Right nephroureterectomy was undertaken. There was an encircling tumour mass, 6 cm distal to the pelviureteric junction and 6 cm in length, obstructing the lumen of the ureter. Microscopic examination showed a signet ring cell adenocarcinoma arising from the epithelium and infiltrating into the muscularis (Fig. 2). The tumour stained positively with PAS-diastase and mucicarmine, and negatively with aldehyde fuchsin. Lymphatic infiltration by nests of malignant cells was also seen in 2 areas. Post-operative chest X-ray, CT scan, gastroscopy and barium enema showed no evidence of further primary malignancy or metastases. Two months later cytology showed a recurrence in the right ureteric orifice. The patient died with lung metastases 12 months after the initial diagnosis.

Comment

Ureteric adenocarcinoma is a rare tumour, with only 17 reported cases. The tumour is usually papillary and only one example of the signet ring



Fig. 1 Right retrograde ureteropyelogram. The renal collecting system is dilated and there is total obstruction of the ureter at the level of L5.

variant has been documented (Ekfors and Nurmi, 1988). The tumour is probably derived from areas of epithelial glandular metaplasia that result from

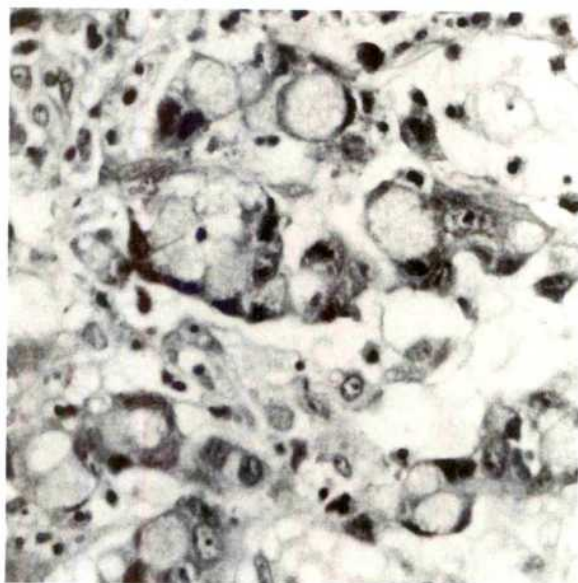


Fig. 2 Section of uretic wall with infiltration by signet ring cell carcinoma. (Magnification $\times 320$).

recurrent mucosal inflammation. Metastatic spread from other primary tumours should be excluded before the diagnosis is made, as a case of gastric signet ring cell carcinoma metastasising to the ureter has been recorded (Stearns *et al.*, 1958).

Tumour recurrence in the ureteric stump is of interest as this is observed in 10% of patients who have undergone ureterectomy and have a previous history of urothelial carcinoma (Brawer and Waisman, 1982). The poor outcome in our patient reflects the aggressive nature of this tumour type and is consistent with the poor prognosis associated with signet ring cell carcinoma of the bladder.

References

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- Stearns, D. B., Farmer, D. A. and Gordon, S. K. (1958). Uret metastasis secondary to gastric carcinoma. *J. Urol.*, **80**, 214-217.

Requests for reprints to B. Delahunt, Department of Pathology, Wellington School of Medicine, P.O. Box 7343, Wellington, New Zealand.

Correspondence

Dear Sir,

Urinary tract infections: the need for pure culture technology in clinical laboratory diagnosis.

Considering the thousands of patients with chronic urinary tract infection (UTI) and its possible advanced stage of interstitial cystitis (IC) (E. G. L. Wilkins *et al.* *Br. J. Urol.*, **64**, 39–44, 1989) currently seeking effective treatment to little or no avail, why is it that these patients continue to receive ineffective identical treatment? The official health agencies that monitor quality control through laboratory inspections have accepted the traditional colony count procedure with no proof of its validity which, I suspect, misleads clinicians into treating fictitious diagnoses. One source (S. M. Finegold and J. B. Baron (eds). (1986). *Rapid screening tests for UTI*. In *Bailey and Scott's Diagnostic Microbiology*. Seventh edition. St Louis: Mosby) indicates that as many as 80% of routine urine cultures are likely to yield only contaminants. The time has long since arrived for the medical community and the diagnostic laboratories to take stock of the magnitude of diagnostic and treatment failures that they may be creating.

For disease entities such as tuberculosis, scarlet fever, gonorrhoea, typhoid and dysentery, the laboratory applies classical pure culture technology to find the index organism which identifies the disease, irrespective of numbers and of all the contaminants that may be present. By contrast, in UTI, the clinical laboratories, using an elementary plate count technology, look for any organisms which, in the technician's judgment, appear in "large enough numbers" and report them to the doctor as causative agents. While other disease entities are identified by a *single* species of bacteria, UTI has been reported due to as many as 17 different species (R. Maskell. *J. Infect.*, **19**, 207–7, 1989) and many more implicated via daily routine diagnostic tests which focus on Gram-negative coliform strains because it is traditional that these strains are "known" to be the main cause. Despite the fact that patients often harbour more than one of these strains at one time or different strains at different times, doctors prescribe "shotgun" antibiotic treatment aimed at these traditional strains, sometimes without having urine tests done at all or regardless of how many strains emerge on culture.

Because of the many treatment failures reported by my patients I have disregarded the Gram-negative bacteria in favour of classical pure culture technology, looking for established pathogens. Results from more than 2600 clinical specimens from over 570 known symptomatic patients nationwide have identified strains of related coccus species (enterococcus and *Gyffkya*) that have emerged in 96% of patients, their significance being supported by the experience that these patients are found in follow-up tests to respond to specific antibiotics rather than agents such as amoxycillin, cephradine or cephalixin.

The critical focus of the new technology (P. Fugazzotto. *Laboratory Management*, **75**, 23–29, 1987) is to culture for urine bacteria after removal of all suppressant urine chemicals from bacterial surfaces and the culture environment by a preliminary washing, since it stands to reason that raw urines (containing waste products, antibiotics and other components varying from patient to patient and which interfere with the emergence of the causative agents) are not valid test specimens. They must have a preliminary "cleansing", as is done in processing sputum for tuberculosis. To accept and process such raw specimens in native form is irresponsible and renders the test grossly biased; there can be no assurance of a valid diagnosis. Bona fide Gram-negative infections have occurred very rarely in this study.

The official agencies must be urged to outlaw the current methods of screen tests and examinations with dipsticks as indicators of possible infection and colony counts on differential agar plates after 24 hours' incubation. These are the basis for the fictitious diagnoses leading to chronic urinary tract infection and possible interstitial cystitis. The laboratories should institute the reliable, well established direct approach of pure culture technology with "wash removal" of urine chemicals for routine testing on all specimens. Clinicians must demand this change in clinical laboratory practice as well as the discontinuance of traditional "shotgun" therapy for "usual aetiological agents" without having a valid laboratory diagnosis with supporting antibiotic panel reports.

Yours faithfully,

P. Fugazzotto
Director (retired), Nevada State Health Laboratory, Rapid City, South Dakota 57701, USA

Notices

British Association of Urological Surgeons

President: R. E. Williams, MD, ChM, FRCS, FRCSE

Annual Meeting: Bournemouth. 21–26 June 1992

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Subcommittee of Council should be submitted on the special forms, which will be available from the BAUS Secretariat in October 1991. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 10th January 1992.

Abstracts not on the special forms will NOT be considered.

All correspondence to: R. J. Morgan, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was made for the first time at the Annual Meeting in Bristol in 1979.

The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes in duration.

Surgery in the Third World

Sir Ian Todd, past President RCSEng, is anxious to build up a list of surgeons in all specialties from the United Kingdom and Northern Ireland (active or recently retired consultant, or higher surgical trainee) who would like to spend some time working and teaching in a third world country.

In most cases accommodation and subsistence are provided and in some air fares also. Periods abroad vary from 1 month upwards but 3 to 6 months are usually preferred.

Please write to Sir Ian Todd, KBE, FRCS, care of the Overseas Doctors Training Scheme Office at the Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN.

Diary

1991

- November 15 Paediatric into Adult Urology. Birmingham. Contact: Miss J. Snowden, Department of Urology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH. Tel: 021 472 1311, Ext. 3287.
- November 15–16 Third Biennial Asia-Pacific Meeting on Impotence, Taipei, Taiwan, R.O.C. Contact: Third Biennial Asia-Pacific Meeting on Impotence, c/o Taiwan Conference Management Co. Ltd, P.O. Box 68–439, 6F–3, 102 Chung Shan N. Road, Sec. 2, Taipei, Taiwan, R.O.C.
- November 21 Controversies in the Management of Prostatic Cancer, St Bartholomew's Hospital. Contact: Dr A. Jelliffe, NETRHA, 40 Eastbourne Terrace, London, W2 3QR. Tel: 071 262 8011.
- November 22–23 International Pelviureteric Junction Obstruction Symposium, Stratford-on-Avon. Contact: Mr P. Shridhar, Department of Urology, George Eliot Hospital, Nuneaton CV10 7DJ.

1992

- January 10 Final date for submission of abstracts for the 1992 BAUS Annual Meeting.
- March 8–13 19th Biennial Congress of the Urological Association of South Africa, Sun City, South Africa. Contact: Dr I. Lissos, 1 Esselen Towers, Esselen Street, Hillbrow, 2001, South Africa.
- March 19–21 Eleventh International Symposium of Operative Andrology. Istanbul, Turkey. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- March 19–21 Searching for Prostatic Carcinoma: the Problem of Screening and Early Detection. Munich, Germany. Contact: D. Née, Secretariat, Department of Urology Krankenhaus der Barmherzigen Brüder, Romanstr. 93, W-8000 Munich 19, Germany. Tel: 89/1793-252 or 89/17 56 61. FAX: 89/1782653.
- March 26–27 Eighth Annual Symposium on Progress in Paediatric Surgery, Oviedo, Spain. Contact: Dr J. L. Teixidor de Otto, Servicio de Cirugía Pediátrica, Hospital Central de Asturias, Centro Universitario, E-33006 Oviedo, Spain.
- April 9–11 6th International Urological Symposium. Girne, North Cyprus. Contact: Dr A. Kelâmi, Brahmsstrasse 32, D-1000 Berlin 45, Germany.
- May 6–8 8th International Symposium on Radionuclides in Nephrourology, The Grosvenor Hotel, Chester, England. Contact: Mr P H O'Reilly, Department of Urology, Stepping Hill Hospital, Stockport, SK2 7JE.
- May 10–14 American Urological Association, Washington Convention Centre, Grand Hyatt, Washington DC.

- May 24–28 Inaugural Meeting of Pan African Urological Surgeons' Association, Harare, Zimbabwe. Contact: Mr A. P. Danso, Department of Surgery, University of Zimbabwe Medical School, P.O. Box A 178, Avondale, Harare, Zimbabwe.
- June 4–6 Fourth International Meeting of Andrology, Como, Italy. "Treating Male Infertility: New Possibilities". Contact: Dr G. M. Colpi, II Divisione di Chirurgia, Centro di Andrologia e Infertilità, Ospedale "VALDUCE", Via Dante 11, I-22100 Como, Italy.
- June 10–12 Continent Urinary Reconstruction. First International Meeting. Lund, Sweden. Contact: Dr Wiking Månsson, Department of Urology, University Hospital, S-22185 Lund, Sweden.
- June 22–25 Canadian Urological Association Annual Meeting, Winnipeg. Contact: Dr R. B. Auld, Suite 620, 5991 Spring Garden Road, Halifax, Nova Scotia, Canada B3H 1Y6.
- June 23–26 BAUS Annual Meeting, Bournemouth International Centre, Bournemouth. Contact: BAUS Office.
- July 22–25 European Association of Urology, 10th Congress, Genoa. Contact: Conference Secretariat, Top Congress—P.R., Piazza Galeazzo Alessi 2/1, 16128 Genoa, Italy.
- August 7–9 Ninth Meeting of International Society for Dynamics of the Upper Urinary Tract. Akita, Japan. Contact: Dr Seigi Tsuchida, Department of Urology, Akita University School of Medicine, 1-1-1 Hondo, Akita, 010 Japan. FAX 81-188-36-2619.
- August 24–27 Third European Symposium on Uroradiology. Herlev, Denmark. Contact Dr H. S. Thomsen, Department of Diagnostic Radiology 54E2, Herlev Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark.
- September 3–6 Tenth World Congress on Endourology and ESWL, Singapore. Contact: Secretariat, c/o Department of Urology, Singapore General Hospital, Outram Road, Singapore 0511.
- September 14–18 Fifth World Meeting on Impotence and Eighth Symposium on Corpus Cavernosum Revascularization, Milan, Italy. Contact: Organizing Secretariat, OMNIA Meeting and Congressi, Via Senato 18, 20121 Milan, Italy.
- October 9–10 BAUS Autumn Meeting, Harrogate. Contact BAUS Office.

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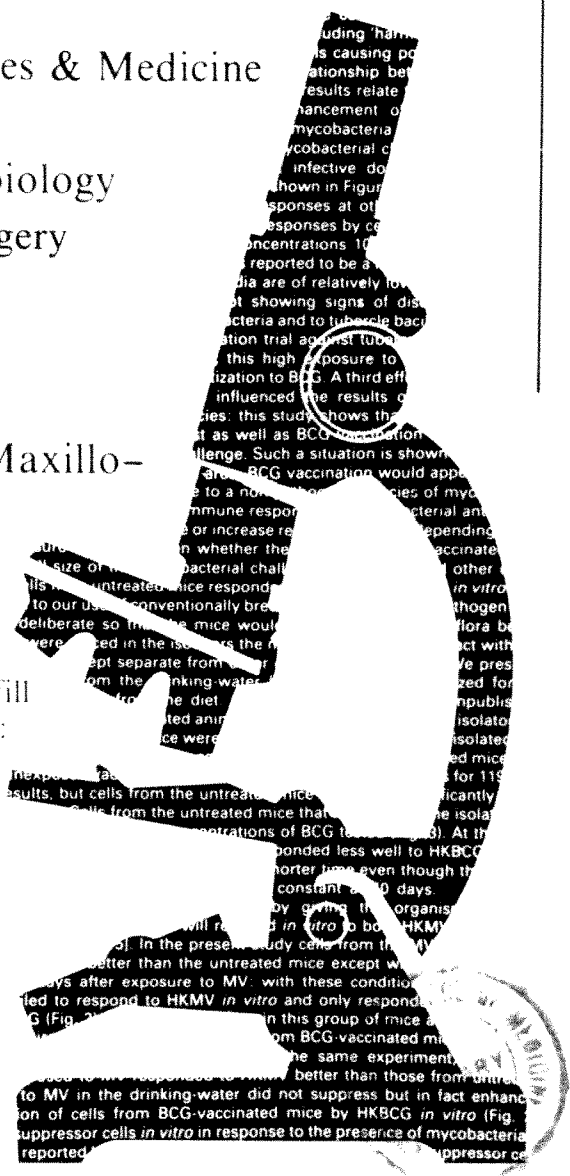
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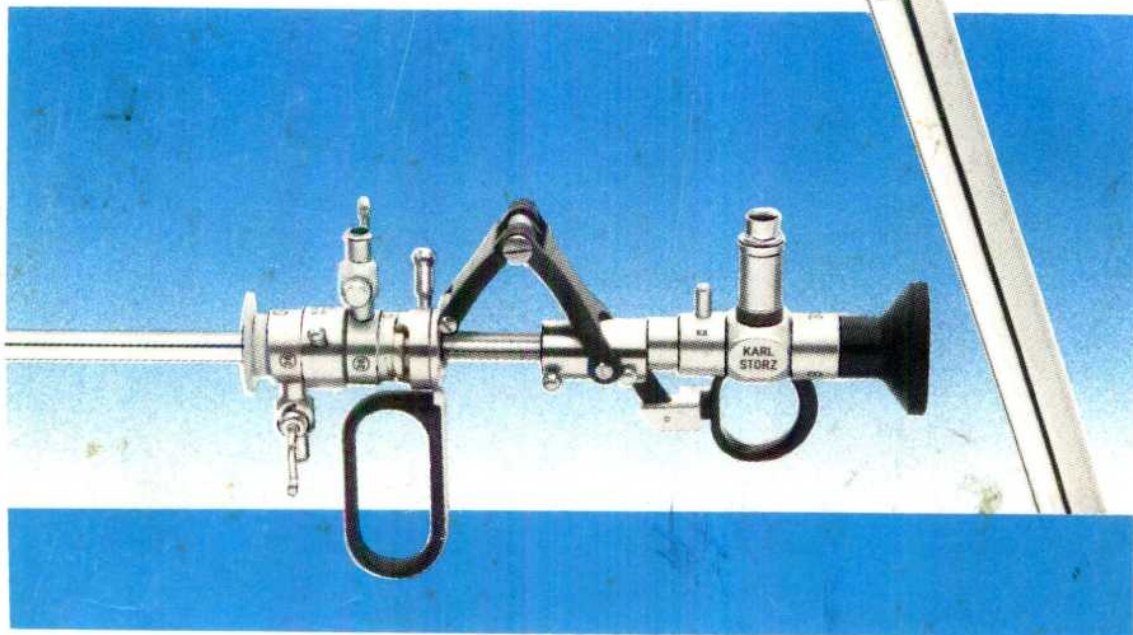
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